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Certified by

Jon W. Dudas

Under Secretary of Commerce
for Intellectual Property
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Patent and Trademark Office

PROVISIONAL APPLICATION COVER SHEET **Mail Stop Provisional Patent Application**

This is a request for filing a PROVISIONAL APPLICATION under 37 CFR 1.53(c).

Docket Number 09013.6001		Type a plus sign (+) inside this box ≡	+

INVENTOR(s)/APPLICANT(s)

LAST NAME	FIRST NAME	MIDDLE INITIAL	RESIDENCE (CITY AND EITHER STATE OR FOREIGN COUNTRY)

TITLE OF INVENTION (500 characters max)

ANALYSIS AND SCREENING OF SOLID FORMS USING THE PAIR-WISE DISTRIBUTION FUNCTION

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ENCLOSED APPLICATION PARTS (check all that apply)

☒ Specification	70 Pages	☐ Small Entity Statement
☐ Drawing(s)	__ Sheets __ Figures	☐ Other (specify)

METHOD OF PAYMENT (check one)

☒	A check or money order is enclosed to cover the Provisional filing fees	PROVISIONAL FILING FEE
☒	The Commissioner is hereby authorized to charge filing fees and credit Deposit Account Number 06-0916.	☒ $160.00 ☐ $80.00 (small entity)

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☒ No.

☐ Yes, the name of the U.S. Government agency and the Government contract number are:

Respectfully submitted,

SIGNATURE _____ Date: February 24, 2004

TYPED OR PRINTED NAME: Steven J. Scott REGISTRATION NO. 43,911

☐ Additional inventors are being named on separately numbered sheets attached hereto.

PROVISIONAL APPLICATION FILING ONLY

Attorney Docket No. 09013.6001

U.S. Provisional Patent Application

for

Analysis and Screening of Solid Forms Using the Pair-Wise Distribution Function

Field of the Invention

This invention relates to the analysis and screening of solid forms. The invention includes the analysis and screening of pharmaceutical compounds.

Background

An assortment of solid forms of a substance can often be generated by solidifying the substance in a variety of different environments. The same pharmaceutical compound, for instance, may be solidified under different conditions to increase the likelihood of obtaining a variety of solid forms of the compound.

X-ray powder diffraction is one of the most direct measurements of the solid form of a substance. Different solid forms exhibit different X-ray powder diffraction patterns. X-ray powder diffraction may be used to distinguish between crystalline solid forms, for instance, by comparing measured peak positions in the X-ray powder diffraction pattern of one sample of a substance to the peak positions measured for another crystalline solid form of the substance.

When performing a screen of solid forms, small amounts of material, for instance < 1mg, may often be used and solidified in each local experiment. With very small amounts of material being measured, each individual powder pattern may represent a less-than-ideal statistical representation of the actual solid structure. Imperfections in the patterns could result from poor particle statistics, preferred orientation, or sample size or placement. It is therefore sometimes difficult to accurately determine whether two X-ray powder diffraction patterns represent the same or different solid forms. Similar problems can also arise even when using larger sample sizes.

A pattern matching technique, disclosed in U.S. patent application no. 10/635,113, filed on August 6, 2003, may be used to group together powder patterns most likely produced from the same solid form. The entire contents of U.S. patent application no. 10/635,113, filed on August 6, 2003, are incorporated by reference herein. In addition, a crystal screening technique, disclosed in U.S. provisional patent application no. 60/514,523, filed on October 27, 2003, may be used to further characterize the powder patterns, including the calculation of their unit cell parameters. The entire contents of U.S. provisional patent application no. 60/514,523, filed on October 27, 2003, are incorporated by reference herein. Amorphous solid forms may also be matched, using general intensity envelopes.

The methods of this invention are also useful in analyzing and comparing two or more materials, even if they are not part of a solid form screen. For example, the methods could be used to determine if a solid form produced from a production run is a disordered form of the desired form, or is a new, unexpected solid form.

Whether part of a screen or not, or whether carried out manually or by a pattern matching computer program, it can sometimes still be difficult to accurately determine whether two X-ray powder diffraction patterns represent the same or different solid forms. Embodiments of the invention described below may be used to assist in determining whether X-ray diffraction patterns represent the same or different solid forms. Additionally, other embodiments of the invention described below can be used to automate the determination of crystal unit cell parameters of solid forms. These embodiments may therefore be used in screens for new solid forms and to distinguish between solid forms.

Summary of the Invention

A first embodiment of the invention comprises a method for determining the crystal unit cell parameters of a solid form.

A second embodiment of the invention comprises calculating and comparing the Pair-Wise Distribution Function (PDF) information obtained for different solid samples to determine whether X-ray powder diffraction patterns of those samples represent the same or different solid forms.

A third embodiment of the invention comprises calculating and comparing the PDF information obtained for different solid samples to determine whether X-ray powder diffraction patterns of those samples are related to each other through disorder.

An fourth embodiment of the invention comprises sorting or screening various solid forms on the basis of PDF calculations specific to the forms.

Further embodiments of the invention are included in the Detailed Description of the Invention, including the generation and use of composite X-ray powder diffraction patterns and the calculation and comparison of PDFs of the composite patterns.

The invention includes the practice of any and all combinations of the embodiments described above and in the Detailed Description of the Invention. For example, the invention includes the practice of the first embodiment, or the first and second embodiment, or the first and second and third embodiment, followed by the practice of any other embodiments. An

embodiment of the invention also includes automating one or more or all of the embodiments discussed above.

The solid forms of the invention include, for example, solid forms of pharmaceutical compounds. The solid forms include forms of salts of compounds, for instance, salts of pharmaceutical compounds. The solid forms include amorphous forms as well as crystalline forms such as cocrystals, hydrates, solvates, polymorphs, dehydrated hydrates, desolvated solvates, molecular complexes, and clathrates. The term "crystalline" includes polycrystalline, microcrystalline, nanocrystalline, mesocrystalline, liquid crystalline, or partially or wholly crystalline substances, as well as disordered crystalline substances. Cocrystals include those disclosed in U.S. provisional patent application no. 60/441,561, filed on January 21, 2003, the entire contents of which are incorporated by reference herein.

The solid forms of the invention may be generated in any manner. For example, a plurality of solid samples of a substance can be generated in capillary tubes or in wells of a well-plate. The samples may be crystallized in different environments, for instance using different solvents, different temperatures, different humidities, or different pressures. Those skilled in the art will appreciate the variety of approaches that may be taken to generate a wide variety of solid forms of a substance.

Some embodiments of the invention include generating an X-ray powder diffraction pattern of solid substances. Those embodiments include, but are not limited to, generating the X-ray powder diffraction patterns while the samples remain in the capillary tubes or in the wells of the well-plate.

Detailed Description of the Invention

A first embodiment of the invention comprises a method for determining the crystal unit cell parameters of a solid form. This method can include the determination of physical constraints derived from knowledge of the molecular structure of the molecules in the solid form. These physical constraints can then be applied to limit the phase space searched by, for example, the Monte Carlo indexing algorithm discussed in U.S. provisional patent application no. 60/514,523, filed on October 27, 2003, to those regions which will allow the molecular structure to fit within the crystal unit cell.

As an example, the molecular formula may be used to determine the real space volume occupied by a single molecule under normal conditions. From the volume occupied by a single

molecule it is possible to predict the expected total volume of the crystal unit cell knowing the number of molecules contained in the asymmetric cell and the multiplicity of each space group being searched. For instance, if the molecule is determined to occupy a volume of 522 A^3 then for a single molecule in the asymmetric unit, the volume expected for a triclinic structure with space group P-1 is $1044A^3$.

As a second example, knowledge of whether a molecular structure is chiral allows the space group search to be limited to only the small subset of space groups that allow chirality. For instance, if a crystalline solid form of a chiral molecule starts to yield index solutions with unit cell volumes twice that of a single molecule, then the structure should either be Monclinic P21 with 1 molecule per asymmetric unit or Triclinic P1 with 2 molecules per asymmetric unit.

As a third example, with knowledge of the structure of a single molecule in a vacuum, it is possible to derive limits for the a, b and c unit cell lattice parameters depending on the number of molecules in the asymmetric unit and the space group multiplicity. For instance, with a single molecule in the asymmetric unit and given the maximum molecular dimension is Dh and the shortest molecular dimension is Ds, then the longest lattice parameter Ch and shortest lattice parameter Cs can be constrained by the following inequalities:

$Ds - 2 < Cs < Ds + 5$

$Ch > Dh - 3$

(Where all integers are in Angstroms).

Apart from the three examples discussed above, one skilled in the art can conceive of the many different constraints that can be derived from knowledge of the molecular structure and applied to limit the phase space requiring searching by the indexing algorithm.

All general space group symmetries may be searched using, for example, the indexing procedure described in U.S. provisional patent application no. 60/514,523, filed on October 27, 2003. Alternatively, only user-specified symmetries may be searched to speed up the procedure. An example of automated indexing of the crystal unit cell appears in Example 1.

For each of the selected indexing solutions, the unit cell can be used to determine reduced structure factors through LeBail fitting of the measured powder pattern. These structure factors can be converted into an electron density image through reverse Monte Carlo methods disclosed in U.S. provisional patent application no. 60/514,523, filed on October 27, 2003. The electron density map can become the final verification that an indexing solution is correct and allows for

the automated selection of a correct solution. Each electron density image can be checked for validity by using a number of selection rules. For example, there should not be any large gaps in the electron density greater than 3 A. There should no multiple overlapping of high-density nodes. Electron density should not be gathered around symmetry points within the unit cell. Clear independent molecules should be visible in the electron density image. The unit cells corresponding to electron density images that satisfy the selection rules are good candidates for correct unit cell solutions. If more that one unit cell solution is selected by this automated procedure, then the different cells can be reduced to identify if they are related symmetries.

A second embodiment of the invention comprises calculating and comparing the Pair-Wise Distribution Function (PDF) information obtained for different solid samples to determine whether X-ray powder diffraction patterns of those samples represent the same or different solid forms. The calculation of the PDF for samples represented by different X-ray powder diffraction patterns can indicate that the samples have the same solid form. Conversely, the calculation of a different PDF for samples represented by different X-ray powder diffraction patterns can indicate that the samples do not have the same solid form. This technique could be applied, for instance, to a screen. In that case, the PDF for each powder pattern generated could be automatically or manually matched to determine which patterns belong to the same forms and which do not. A subsequent step could involve comparing the PDF of one or more of the forms to the PDF of a known form or forms to determine whether any of the forms produced are new. An example of calculating the PDF in pattern of a solid sample appears in Example 2.

A third embodiment of the invention comprises calculating and comparing PDF information calculated for two different solid samples to determine whether the X-ray powder diffraction pattern of one sample represents a disordered version of the same solid form found in the other sample. When matching PDF transforms between crystalline and disordered crystalline material, the range of the PDF transform in real space should be truncated to below the average crystal size in the disordered material in order to maximize the match score. Inspection of the PDF transform from the disordered material can identify the maximum real space range to be matched. The maximum range is set to the real space distance where the PDF transform for the disordered material falls to a flat zero line. Typically for most small and medium organic molecules this distance is between 15A and 30A for very disordered material. An example of

the use of PDF in establishing order-disorder relationships between patterns appears in Example 3.

A fourth embodiment of the invention comprises sorting or screening various solid forms on the basis of their calculated PDF. For instance, the invention comprises a method of screening for new solid forms of a substance, which comprises determining the PDF for each of a plurality of samples of a substance using the embodiments described above, comparing the PDFs of the samples to the PDFs of known solid forms of the substance, and identifying those samples that have a PDF different from that of the known solid forms.

If certain individual powder patterns have a number of diffraction peaks in common, they could be manually or automatically matched and then averaged, leading to a composite pattern. Automatic pattern matching could be performed using the pattern matching techniques disclosed in U.S. patent application no. 10/635,113, filed on August 6, 2003. A further embodiment of the invention comprises calculating the PDF of such a composite pattern. This could be followed by a second pattern matching on a set of these PDFs to determine if any groups should be consolidated. The invention also includes the step of comparing the PDFs of composite patterns to known PDFs to determine if a new solid form has been found.

Another embodiment of the invention includes manually or automatically matching patterns and arranging the members of each group in the order of how well they match. The PDFs of the best match and the worst match in each group can be calculated and compared to indicate whether all group members have the same solid form.

Example 1

In an embodiment of the invention, an indexing method is used that is similar to the one described in U.S. provisional patent application no. 60/514,523, filed on October 27, 2003, with some differences illustrated below.

Rather than depend on the user's knowledge of the molecular weight and volume of the solid form being indexed, this method simply requires as input the chemical formula of the form in question. The method uses the chemical formula to calculate an estimate of the unit cell volume by looking up the volume for each different atom, multiplying it by the number of those atoms present in the formula and then adding them all up. For example, H_2O contains two hydrogen atoms (each with a volume of 5.08) and one oxygen atom (volume 11.39) giving it a total volume estimate of $2 \times 5.08 + 11.39 = 21.55$. The final minimum and maximum volume

bounds used in indexing might use the estimated number plus or minus a certain percentage, for instance 10-20%.

The general space group symmetry may or may not be specified. In the latter case, the method can automatically search all symmetries. Additionally, all relevant multiplicities can be searched for each symmetry. The aim of indexing is to derive the crystal unit that best describes the measured X-ray peak positions using the smallest unit cell volume and highest general symmetry. By searching specific space groups in a specific order it is possible to ensure that the first set of solutions found will correspond to the highest symmetry and lowest volume. For example, the method may search the symmetries in the following order: Orthorhombic (4), Monoclinic (2), Triclinic (1), Orthorhombic (8), Monoclinic (4), Triclinic (2), Orthorhombic (12) etc through increasing multiplicity. The integer in parentheses after the general symmetry is the multiplicity of the molecule. Within each general symmetry are the specific space groups allowed by the molecule. For example, an organic chiral molecule will typically occupy Orthorhombic space groups P212121 and P21212 with a multiplicity of 4. The method may, at the option of the user or automatically, decide to stop after a solution is found or proceed looking for a better solution in other symmetries/multiplicities. Better solutions with higher volumes may later be reduced to the equivalent symmetry with smallest volume.

Example 2

In an embodiment of the invention, the PDF may be used to compare two X-ray powder diffraction patterns to determine whether those samples represent the same or different solid forms. By definition, the atomic pair distribution function PDF is the instantaneous atomic density-density correlation function, which describes the atomic arrangements in materials. It is the sine (imaginary) Fourier transform of the experimentally determined reduced structure factor obtained from a measured powder pattern. Since the total structure factor contains both the Bragg intensities and the diffuse scattering its Fourier associate, the PDF, yields both the local and average atomic structure of materials. In contrast, an analysis of the Bragg scattering intensities alone yields only the average crystal structure. Determining the PDF has been an approach for characterizing glasses, liquids, amorphous solids and random alloys for some time. However, its application to screening of materials is new.

Typically, it is expected that neutrons - as opposed to x-rays - give the best measure of the PDF, due to the very large momentum transfers possible. However, it has been found that

high intensity x-ray sources may also be useful as they can give significant x-ray intensity levels even out to the largest measurable Q values. Laboratory sources often may not be very useful for a typical PDF analysis due to the small Q range that can be usefully measured. Fortunately, it turns out that for medium and large organic molecules, for instance, laboratory x-ray sources are sufficiently sensitive to derive a PDF. To achieve this the PDF reconstruction in real space must be enhanced.

The first step is the calculation of the reduced structure factor S(Q) from the measured powder pattern. All instrumental and known thermal contributions to the measured intensity should be removed from the measured intensity along with the true instrumental background. Removal of the background is desired as one should not remove any diffuse scattering or broad intensity features generated by the sample of interest.

The instrumentally corrected data is converted into Q-space and then reduced to remove the average electronic form factor. The strong electronic form factor present in molecular organic materials is the primary reason why data only needs to be measured out to 40 or 60 degrees 2theta and why standard laboratory sources are sufficient. The removal of the electronic form factor gives the total structure factor S(Q).

$S(Q) = 1 + [Ic(Q) - \text{sum}(c_i\ f_i(Q)^2)] / \text{sum}(c_i\ f_i(0)^2)$

Where Ic(Q) is the corrected measured data as a function of Q, c_i is the concentration of each atom type present and $f_i(Q)$ is the individual atomic form factor.

This form factor expression can be very difficult to evaluate for large organic molecules and is therefore often approximated by:

$\text{Sum}\ (c_i\ f_i(Q)^2) \Longrightarrow \text{weight}\ \exp(-Q^2/\text{width})$

With the values for weight and width being selected automatically to provide a reduced structure factor F(Q) which asymptotically approaches zero at large values of Q.

$F(Q) = Q * [S(Q) - 1]$

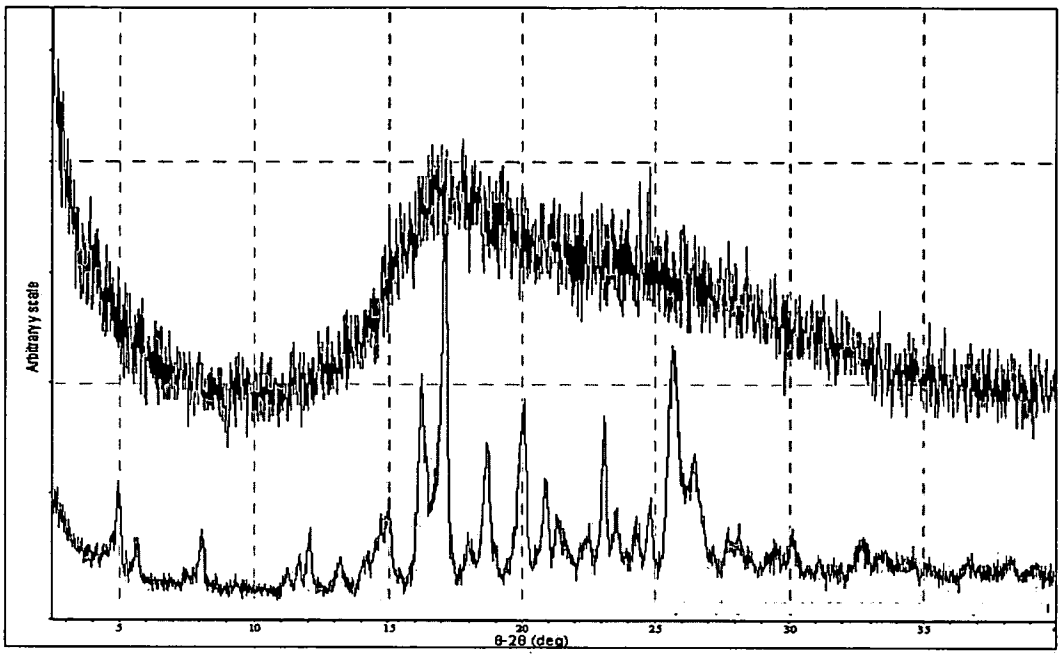
Once the operator or algorithm has validated the nature of the reduced structure factor, then the PDF transform can be applied.

$PDF = G(r) = Sum(F(Q_i)*sin\ (Q_i*r_i))$

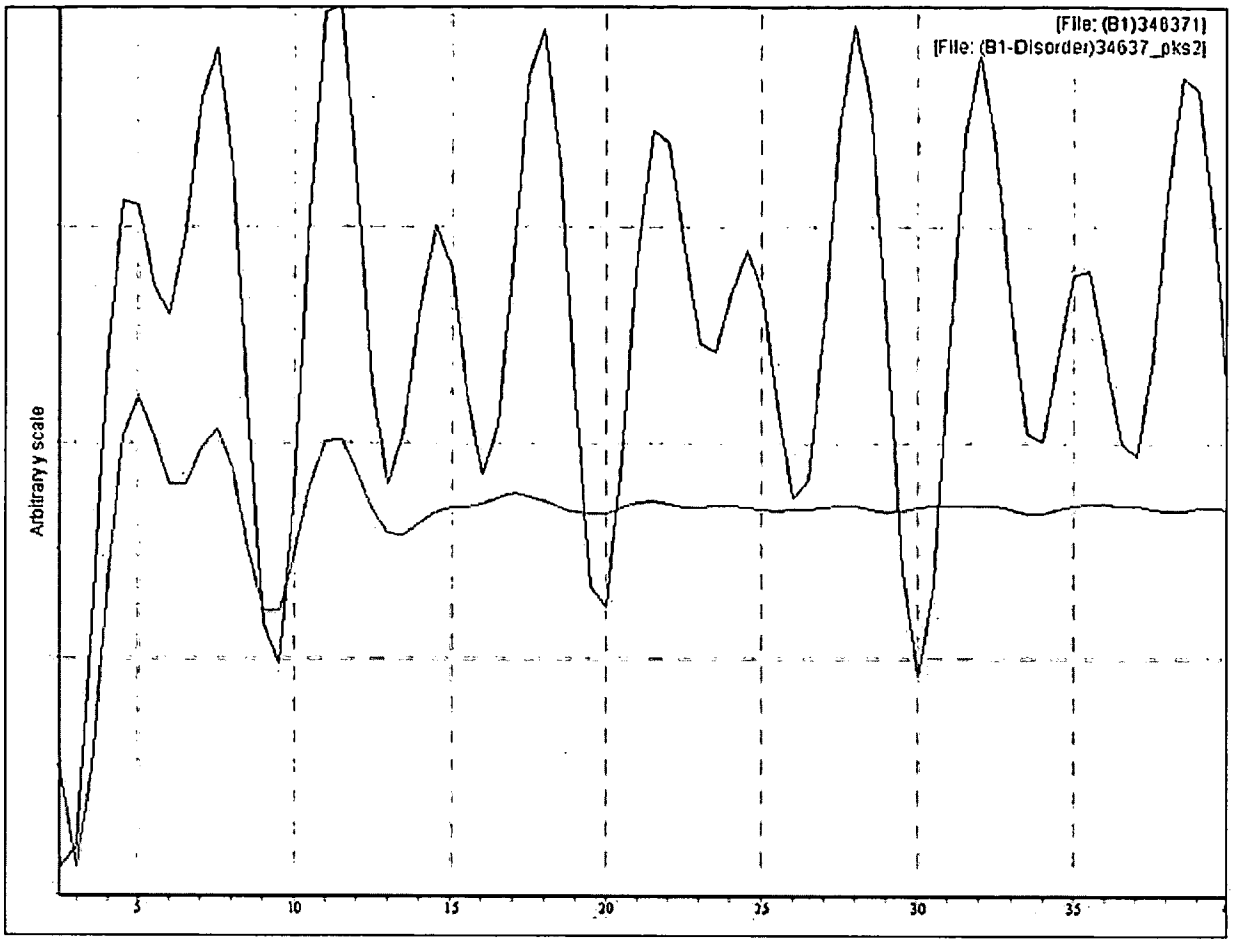
In order to enhance the resolution of the PDF function in real space "r", the sin transform is evaluated over an artificial range of 'r' values not determined by the measurement range. For example, the PDF can be reconstructed using an 'r' step size of 0.2 A which is equivalent to measuring out to 180 degrees 2Theta using an x-ray wavelength of 1.0A. The resulting PDF is reconstructed over the range of inter atomic distances of interest and displayed in real space Angstroms. Peaks in the PDF function correspond to instantaneous atom-atom density correlations and they can be compared to determine if the two patterns are likely of the same solid form. Moreover, peaks within the PDF transform typically contain information on the most likely unit cells that describe the periodic structure of the crystalline lattice being measured. These peak distances can be used as input for unit cell parameters in the indexing algorithm providing further phase space constraints.

Example 3

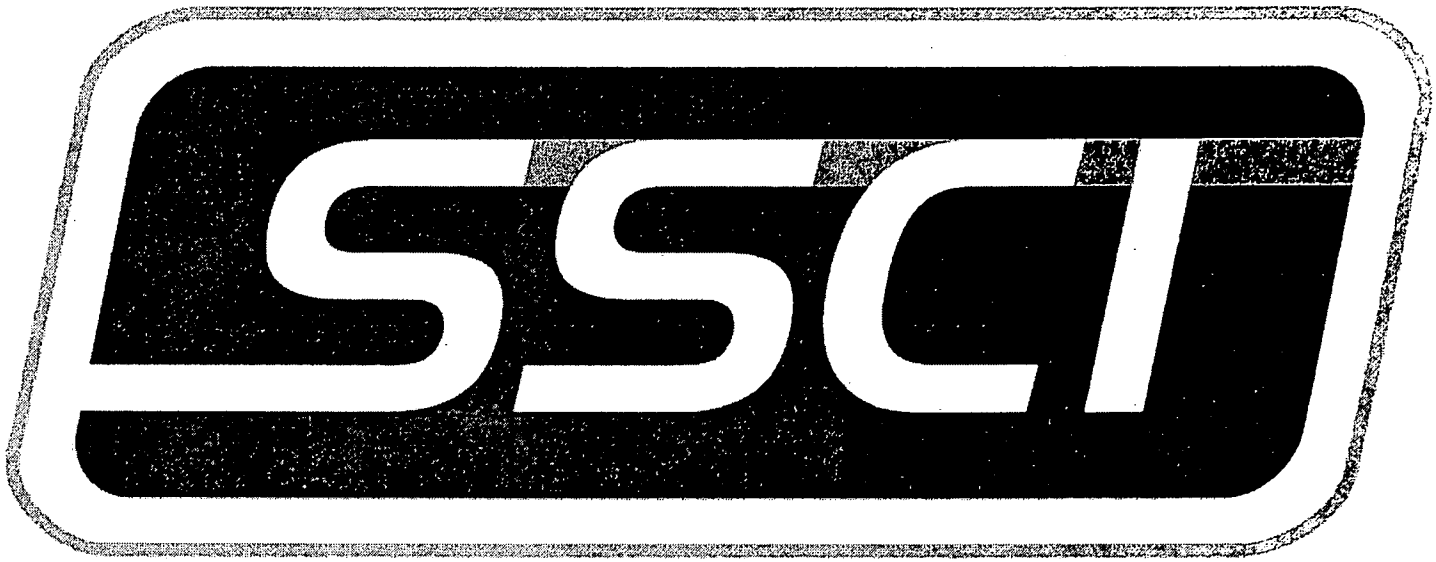
In an embodiment of the invention, the PDF may be used to compare two X-ray powder diffraction patterns to determine whether one of the samples is a disordered version of the same solid form. It is often possible to produce crystalline forms from disordered forms so it is useful to know which crystalline form is the parent of the disordered one. The figure below illustrates a typical disordered pattern and how it compares to a highly crystalline one. It is difficult to determine the exact relationship between the two purely through visual inspection of the X-ray powder diffraction data, as the peaks in the disordered pattern are too broad.



Upon applying the PDF to both patterns, we get the following picture which clearly illustrates that the two forms are in fact related. The top pattern is the PDF of the highly crystalline form while the bottom is the PDF of the disordered pattern. One might observe that the peaks below 20 A match well. After that, the disordered pattern loses long range order, which is indicative of the fact that the crystal size for the disordered material is probably around 20 A and that the disordered material contains small crystals of the same solid form that produced the other pattern.



Although the invention has been illustrated by the preceding examples, it is not to be construed as being limited to the materials or techniques employed therein. Various modifications to these examples can be made without departing from the spirit or scope of the invention.



Analysis of Disordered Materials using XRPD and PDF transform:

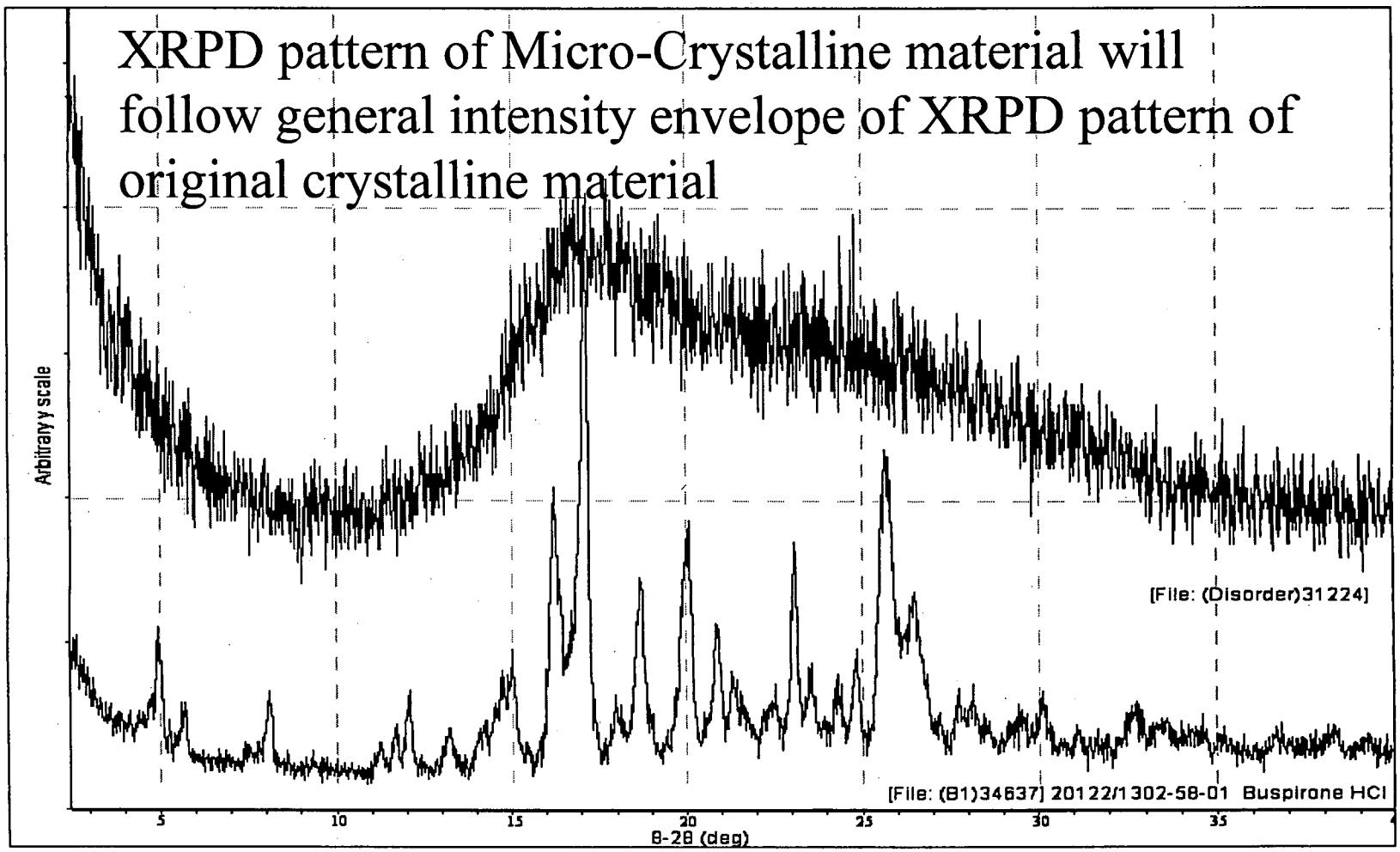
Micro-Crystalline - True Amorphous?

Analysis of Disordered Materials using XRPD and PDF transform

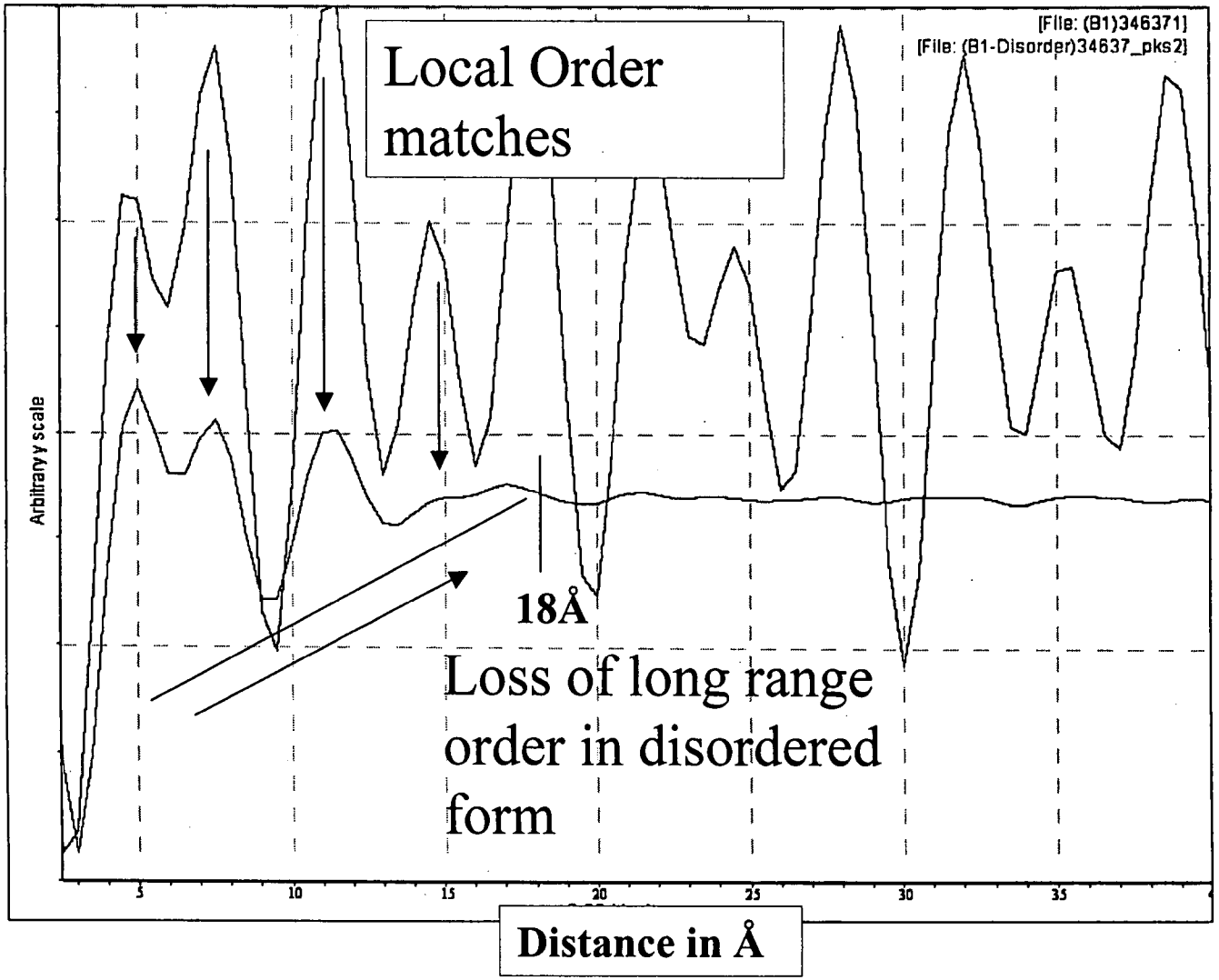
- Cryo-Grinding of Crystalline Material to give Micro-Crystalline Material (Buspirone)

- Cryo-Grinding of Crystalline Material to give Amorphous material (Indomethacin IMC).
  - Reference: **Crowley & Zografi: J. Pharm. Sci. 91, 2, 2002**

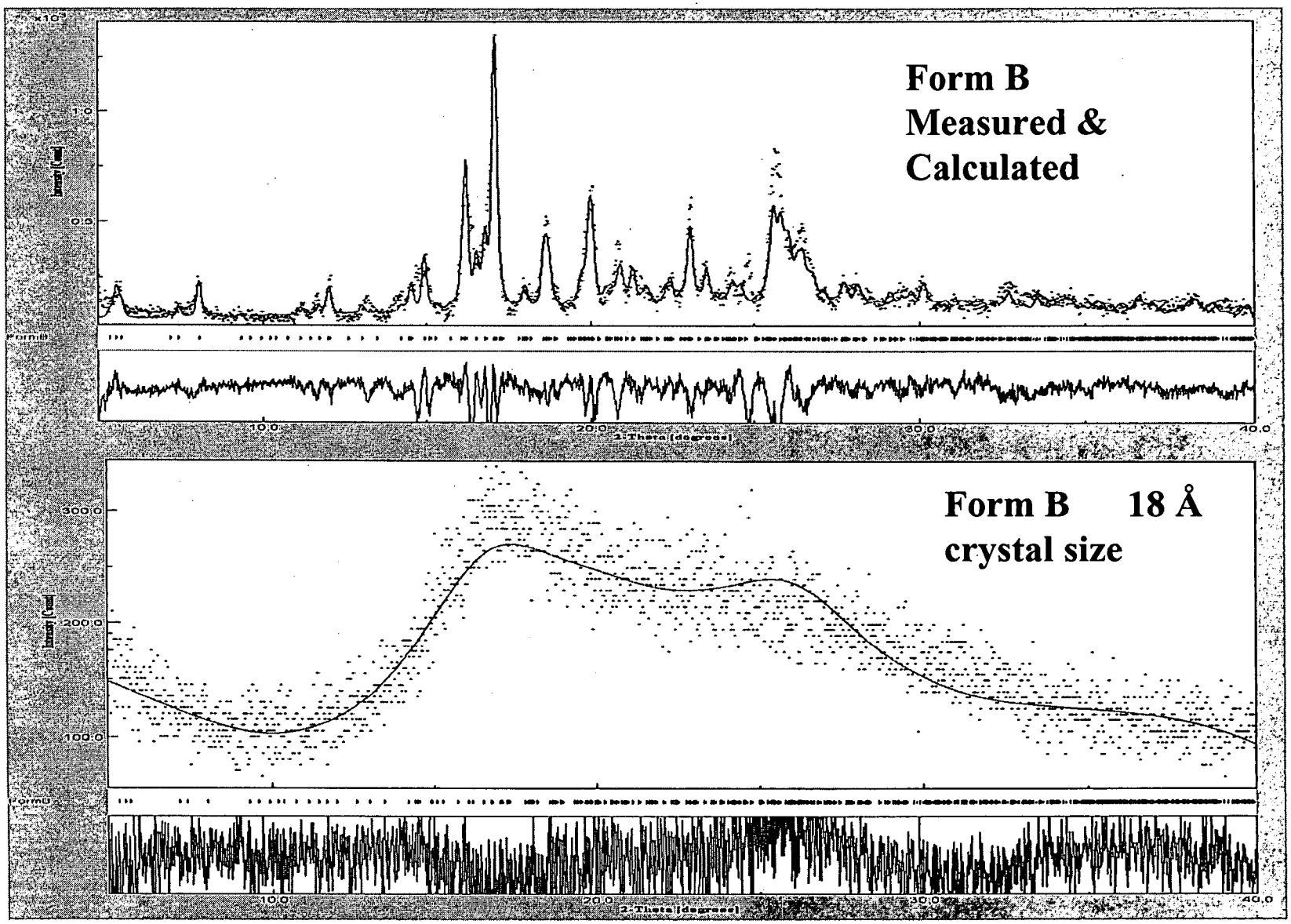
XRPD Pattern Analysis - PDF & Micro-Crystalline Material



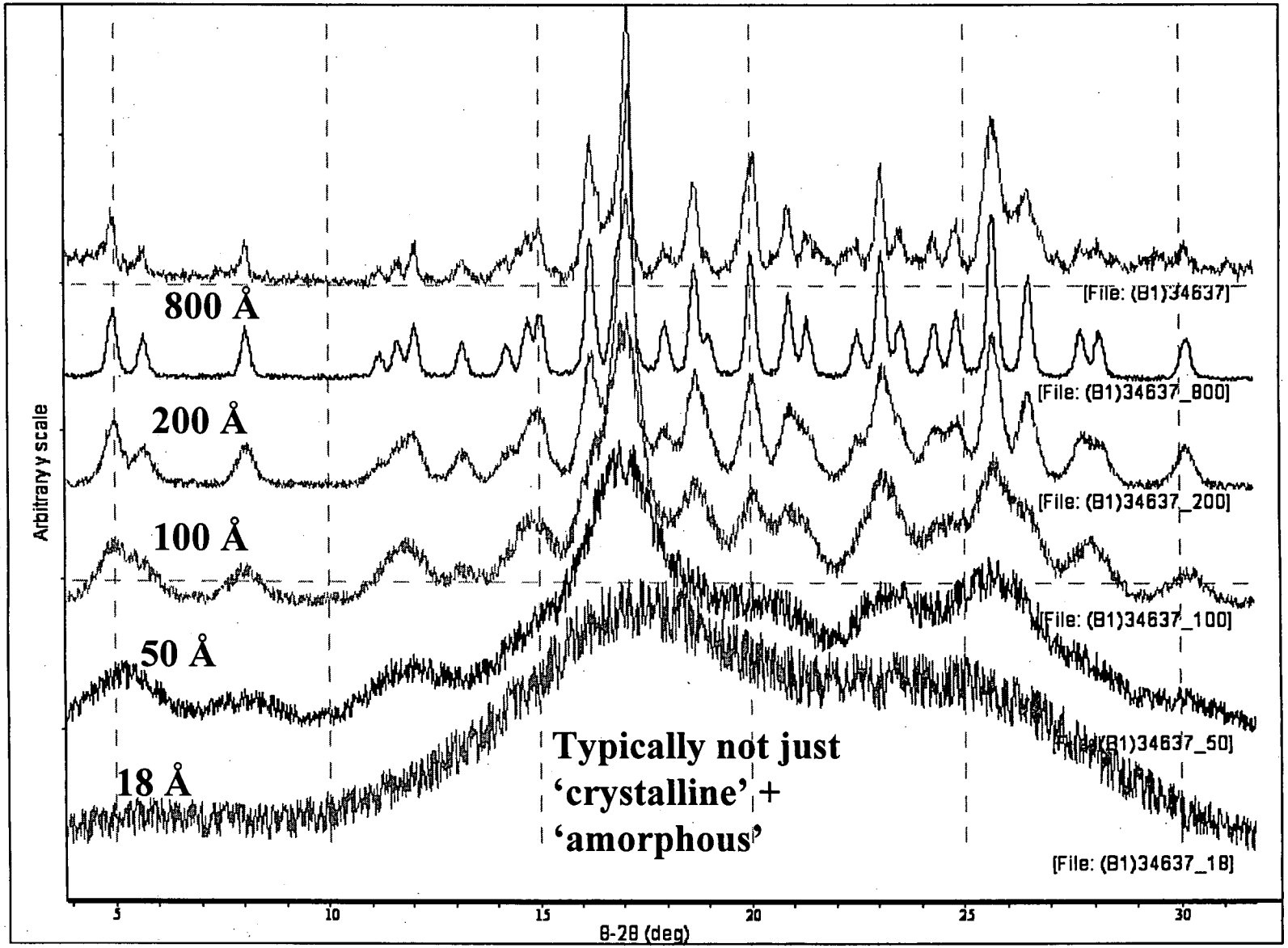
XRPD Pattern Analysis - PDF & Micro-Crystalline Material



XRPD Pattern Analysis - Rietveld & Micro-Crystalline Material



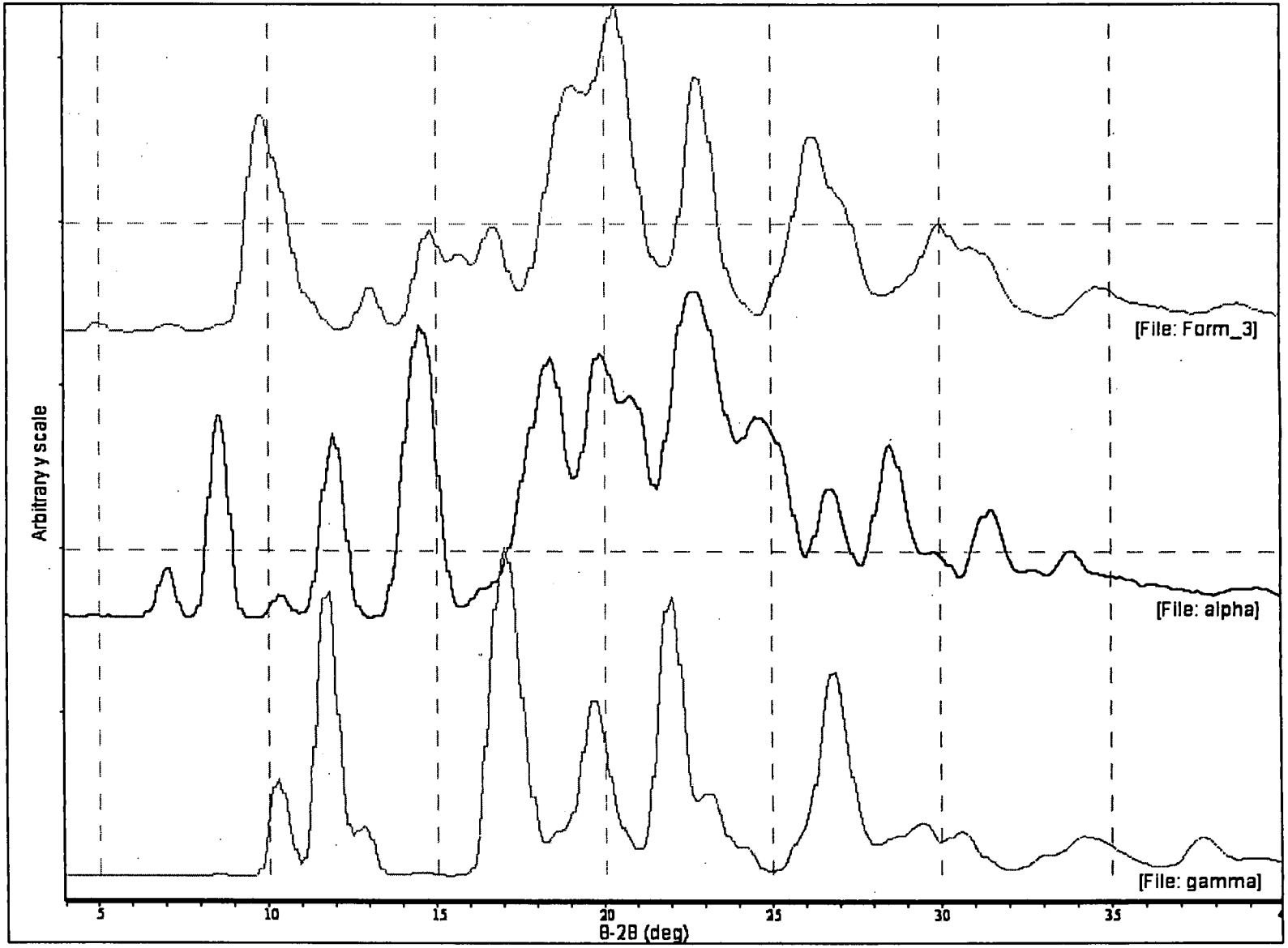
XRPD Pattern Analysis: multi-length-scale Micro-Crystalline Material



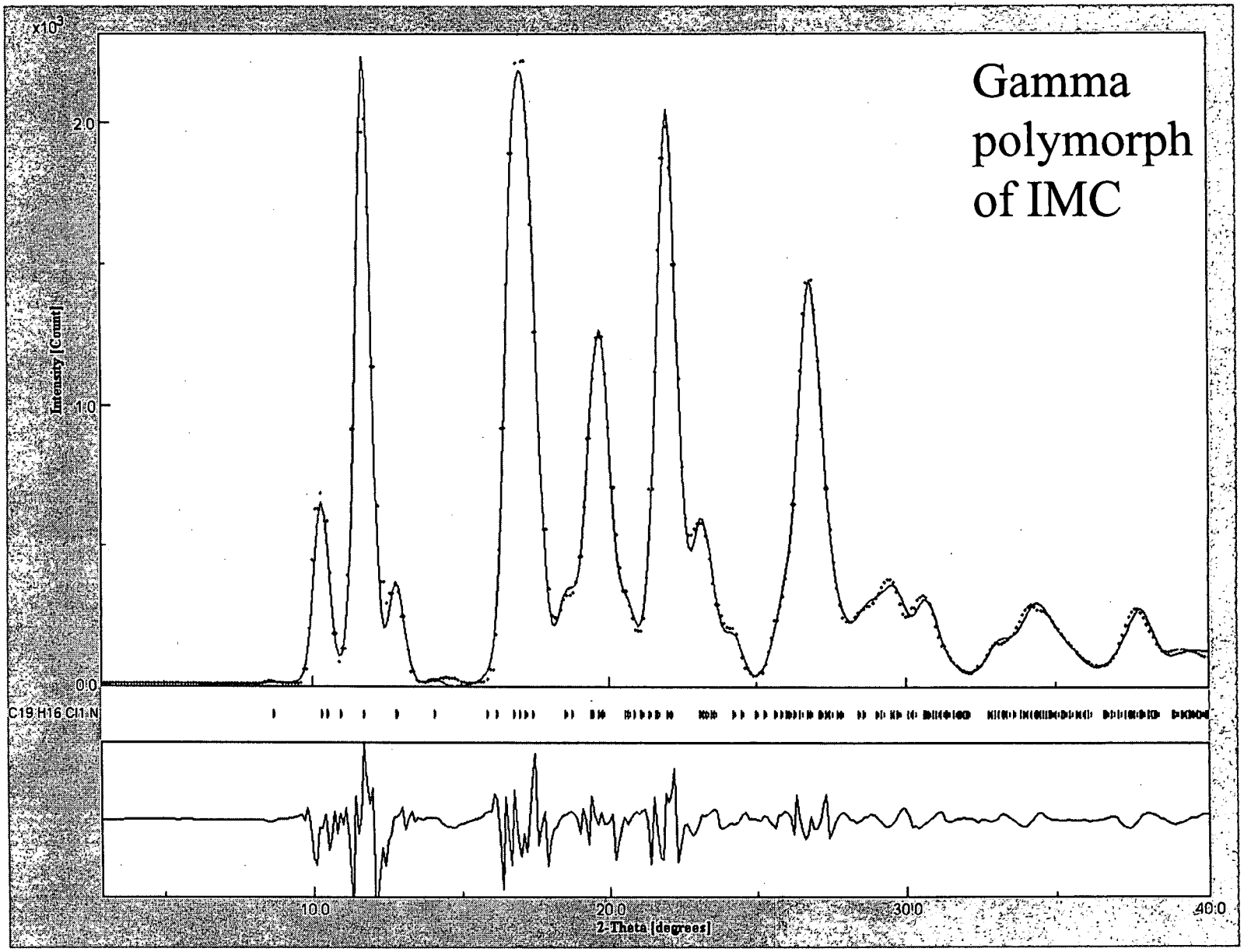
Grinding of Crystalline Material to give Micro-Crystalline Material

- Cryo-Grinding crystalline material most likely leads to micro-crystalline material.
  - Reduced crystallite size --> N-N molecular distances. (Really nano-crystalline)
  - Increase of random spatial location of molecule (strain: micro and thermal)
  - Local short range molecular order retains same character as original crystalline material..
  - Thermodynamically unstable with relaxation times similar in nature to 'amorphous' material

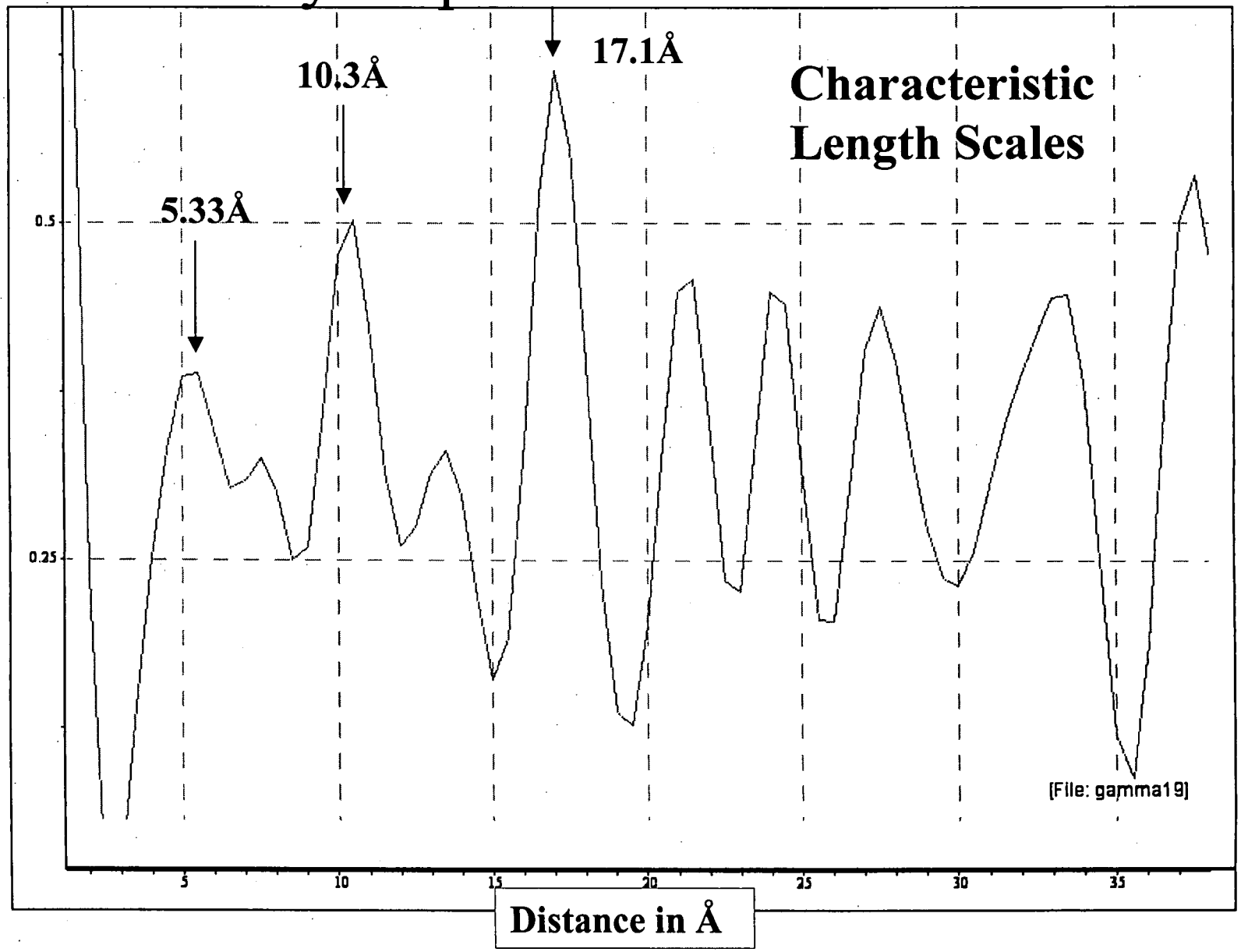
XRPD Pattern Analysis: Crystalline XRPD patterns for 3 polymorphs of IMC

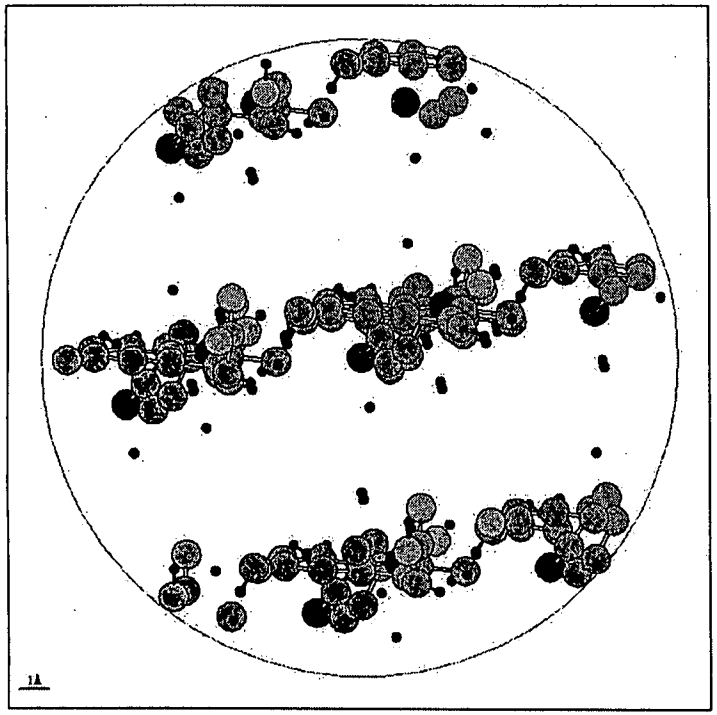


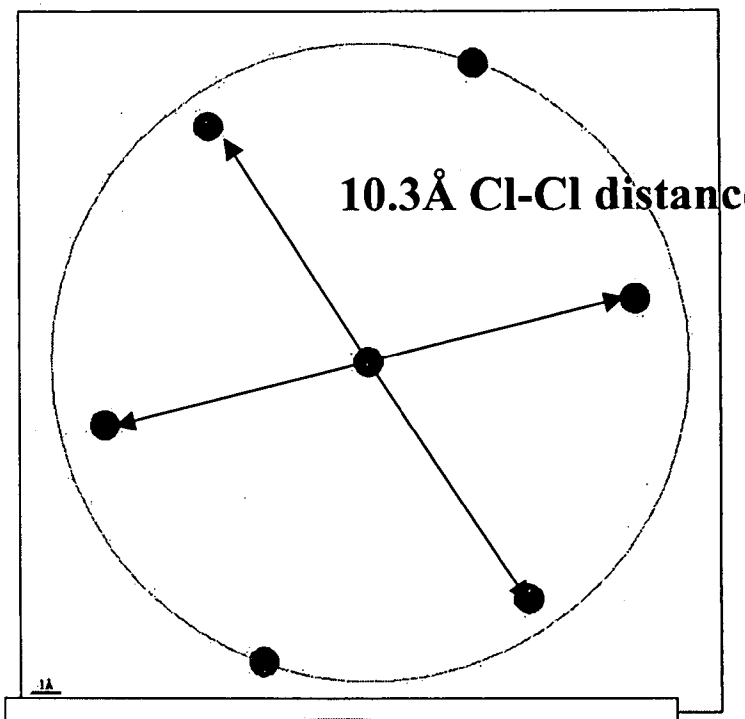
XRPD Pattern Analysis: Measured and Calculated Form Gamma



XRPD Pattern Analysis: PDF Transform of Gamma Polymorph of IMC



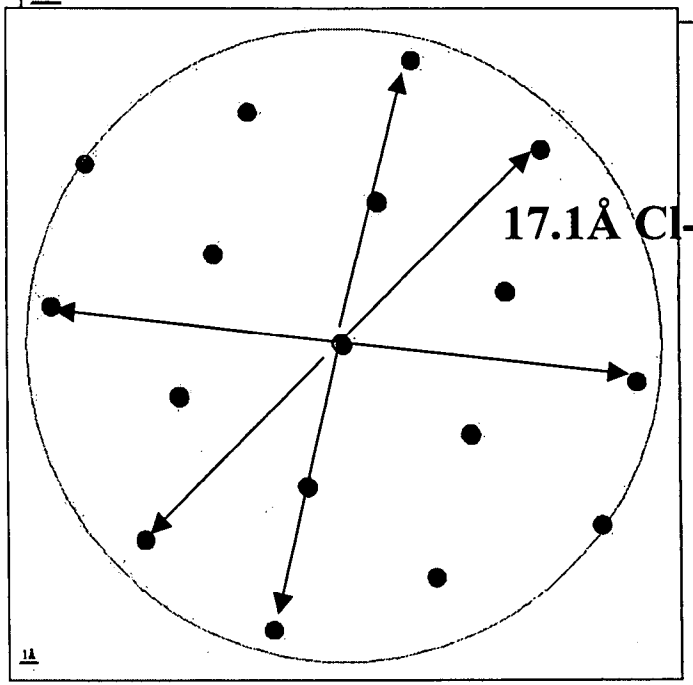




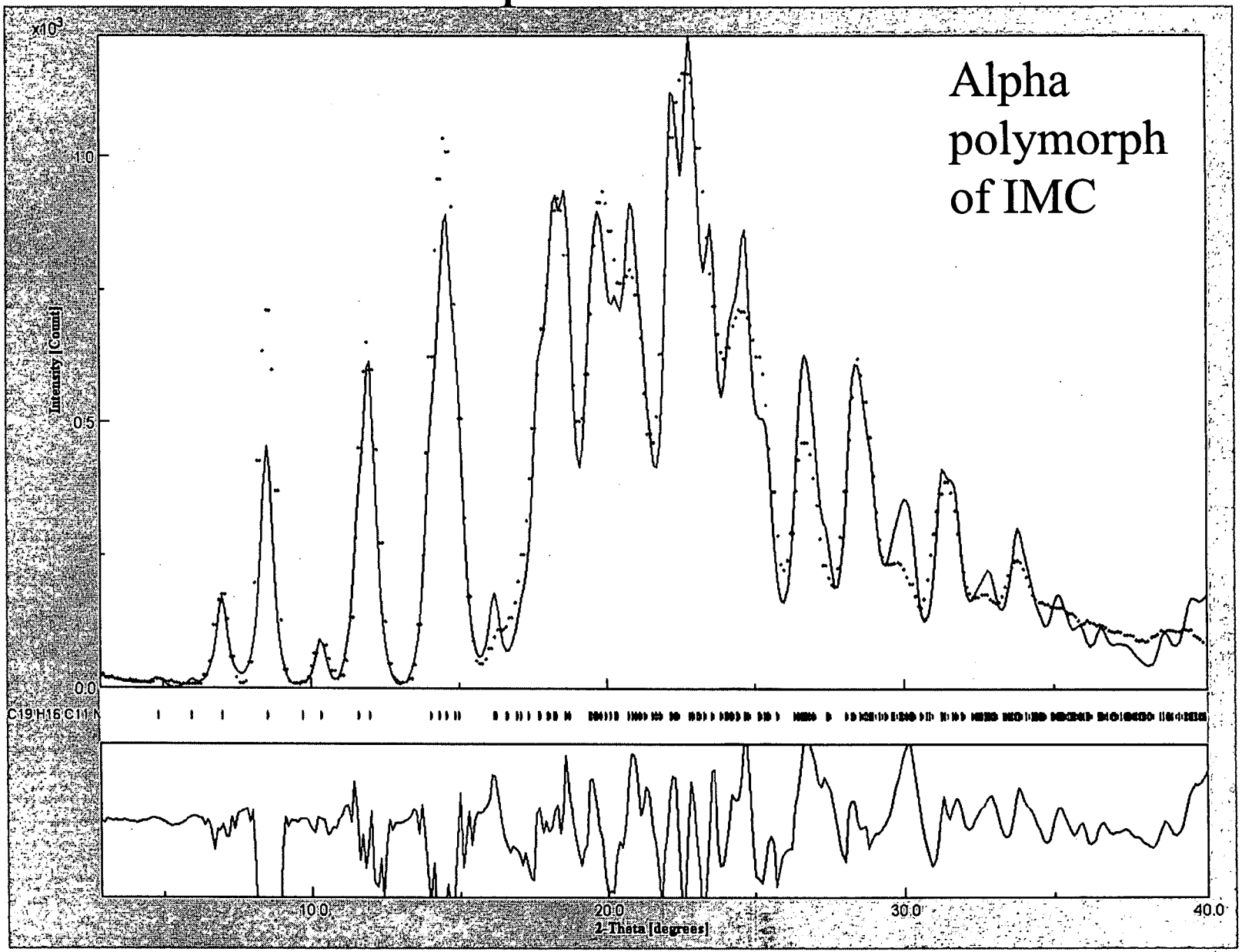
Form Gamma

View of crystal structure for Gamma form using Cl as a central atom.

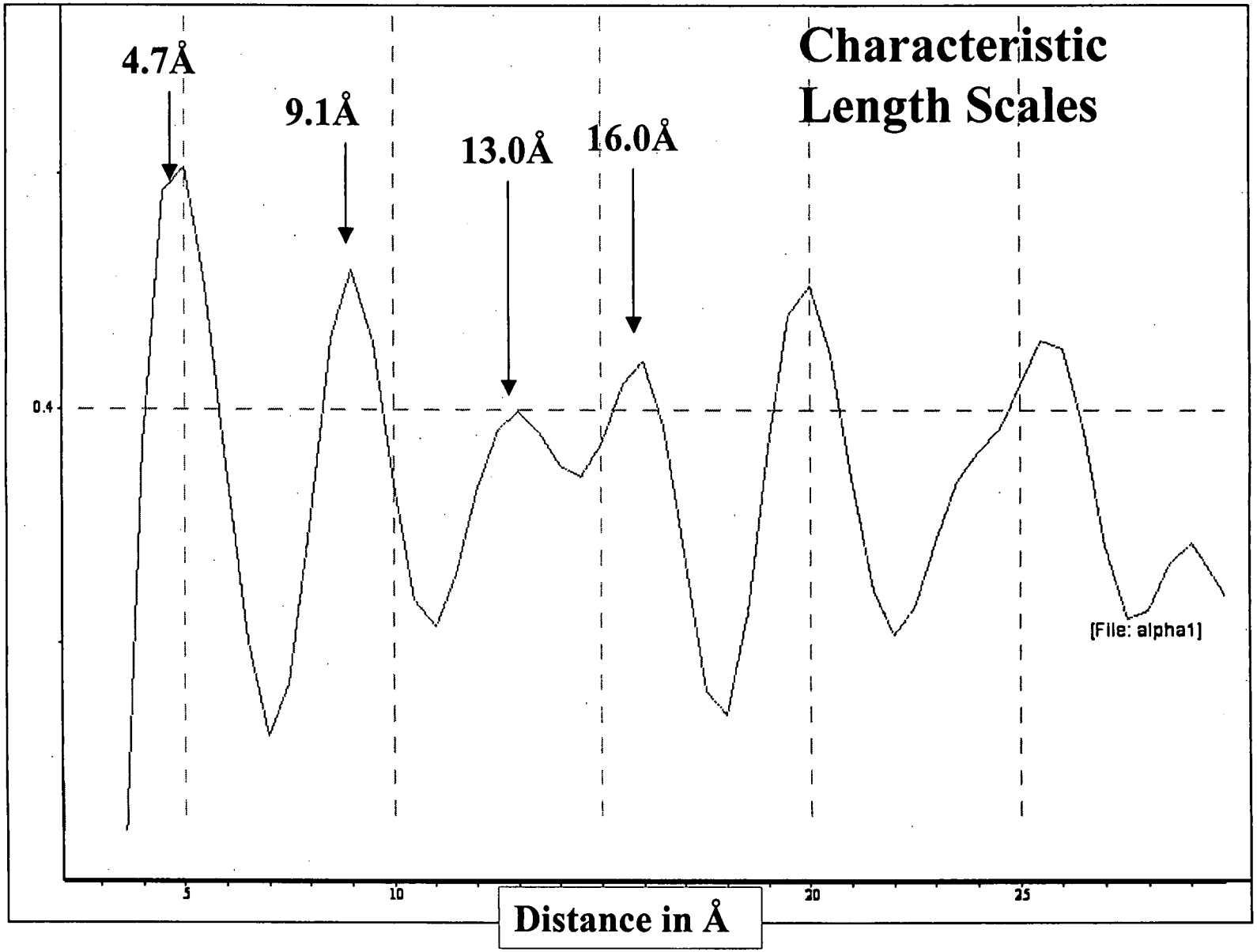
Cl forms a very simple lattice acting as a frame for the organic components.

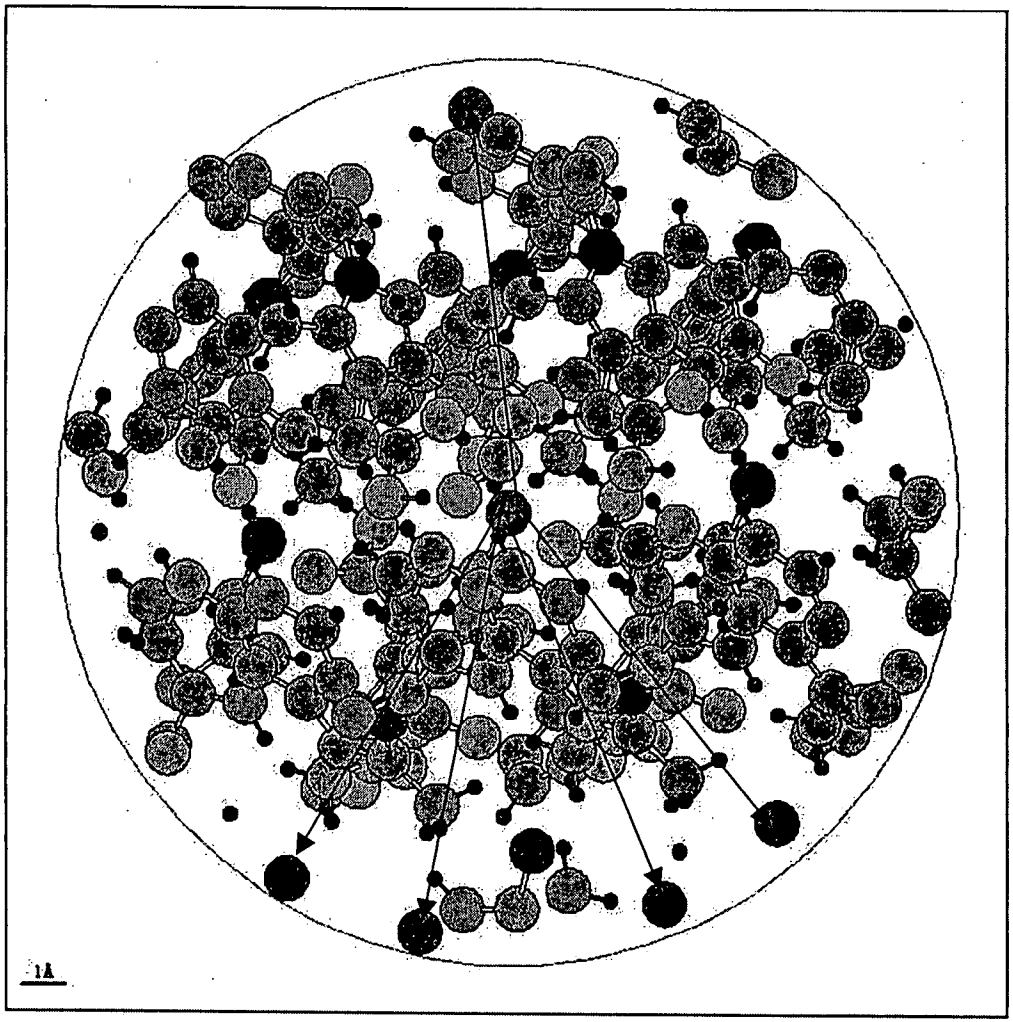


XRPD Pattern Analysis: Measured and Calculated Form Alpha

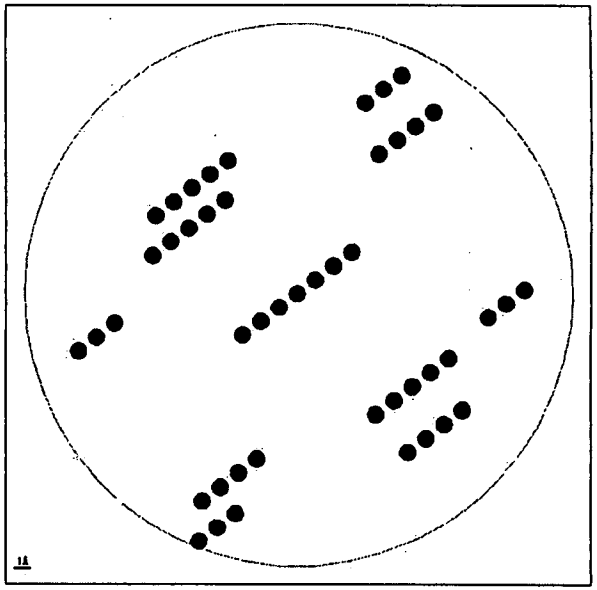


XRPD Pattern Analysis: PDF Transform of Alpha Polymorph of IMC





9.3 Å Cl-Cl distances

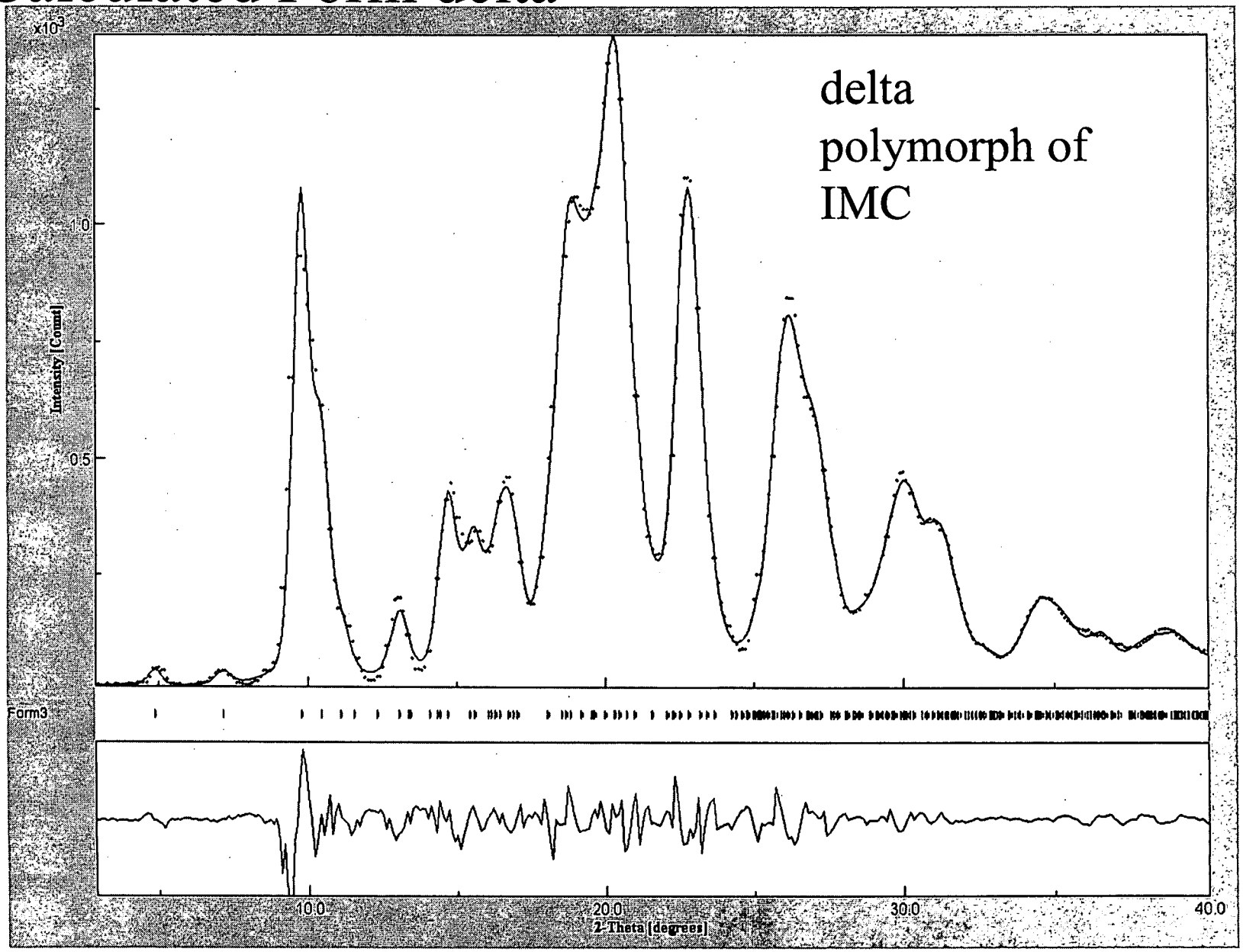


View of crystal structure for alpha form using Cl as a central atom.

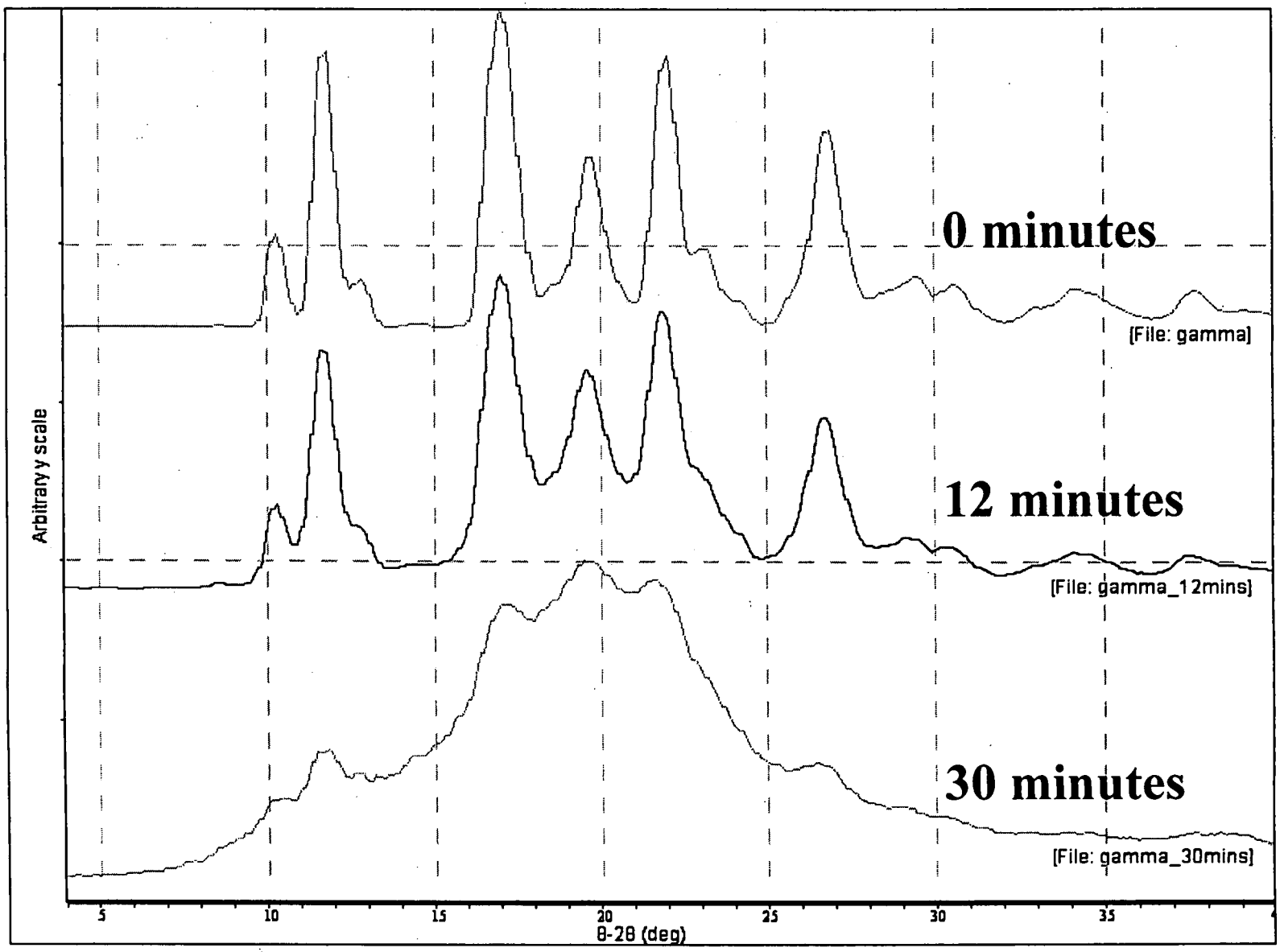
Cl forms a very simple lattice acting as a frame for the organic components.

Form Alpha

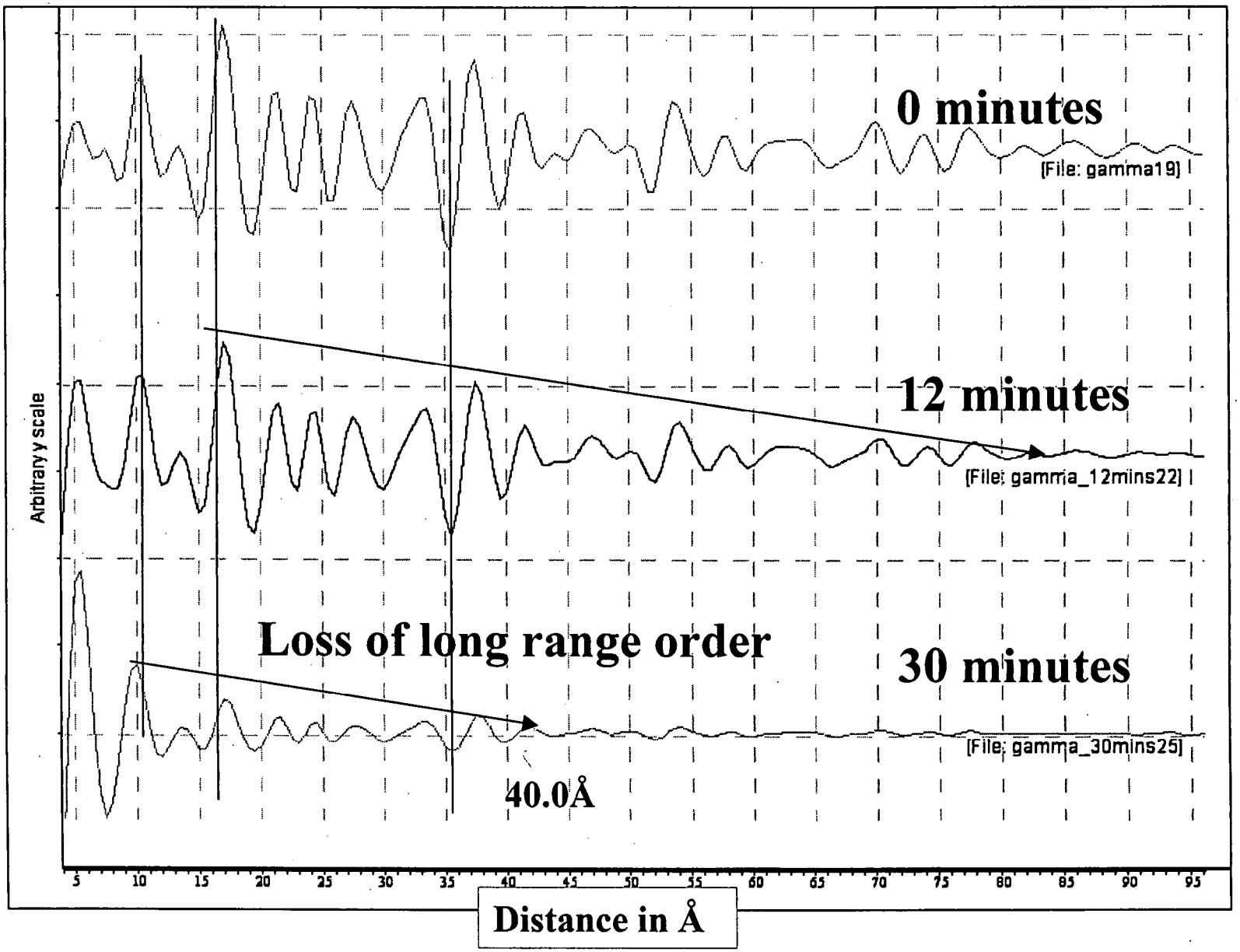
XRPD Pattern Analysis: Measured and Calculated Form delta



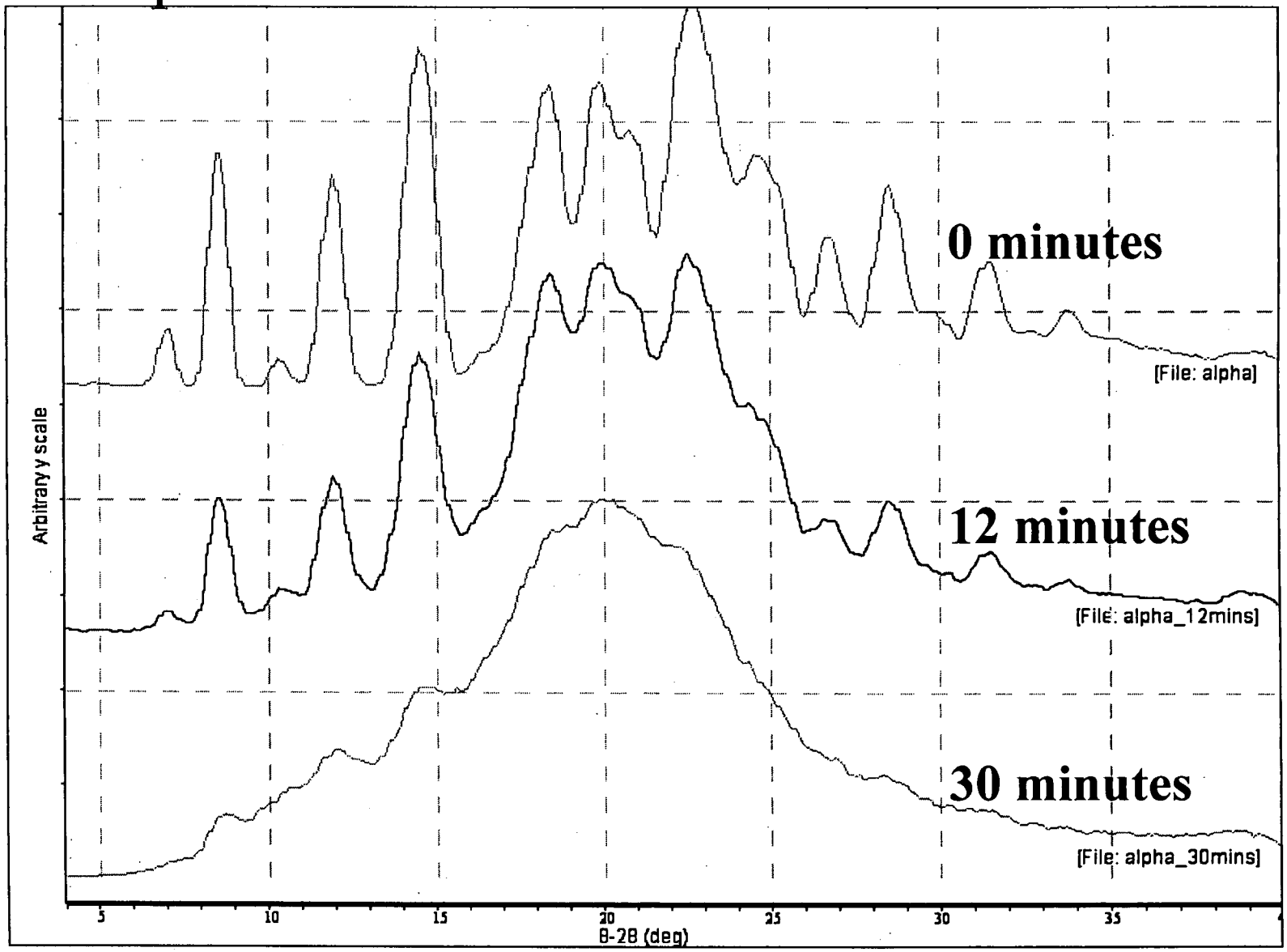
XRPD Pattern Analysis: Cryo-Grinding of Gamma Form



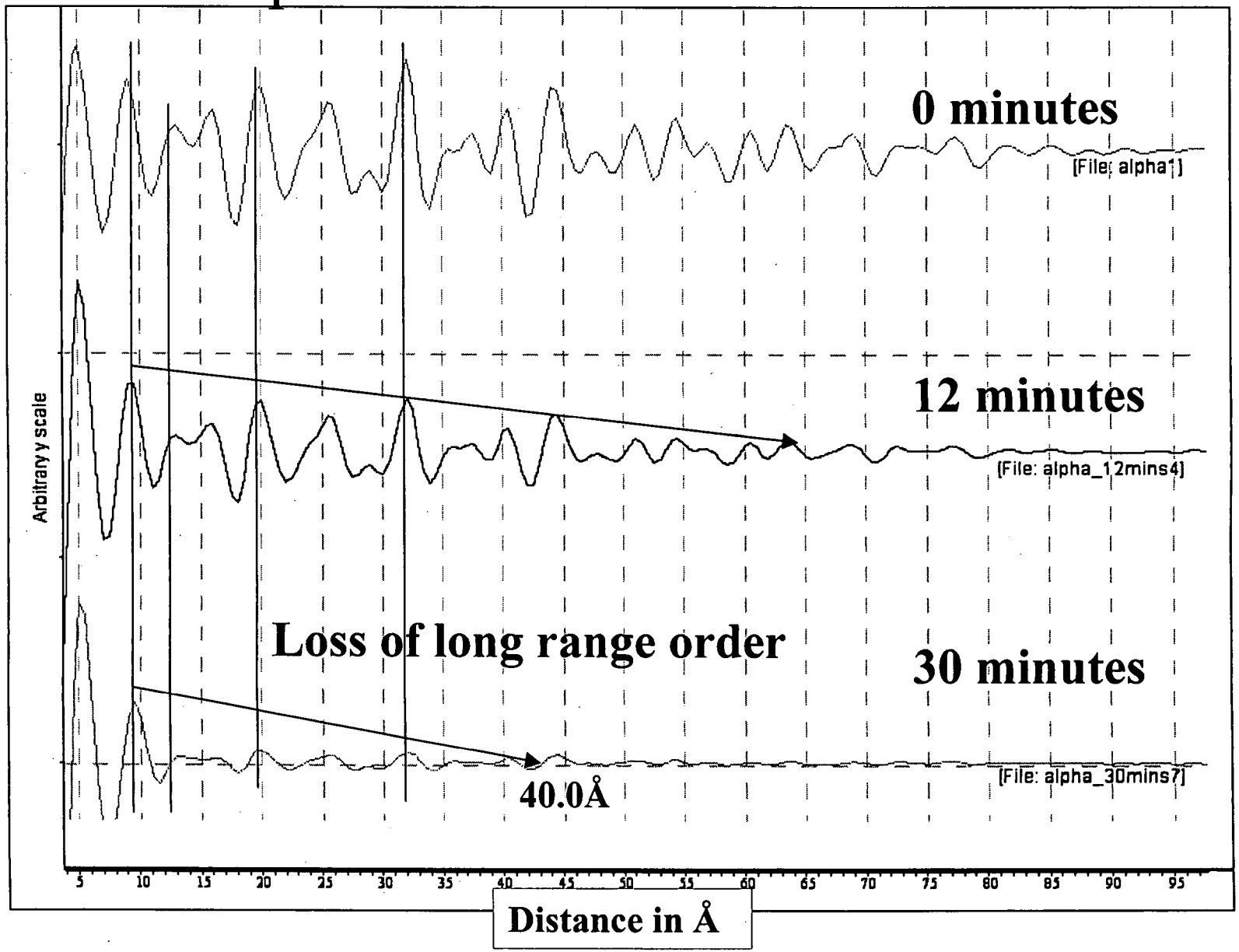
XRPD Pattern Analysis: PDF of Cryo-Ground Gamma Form



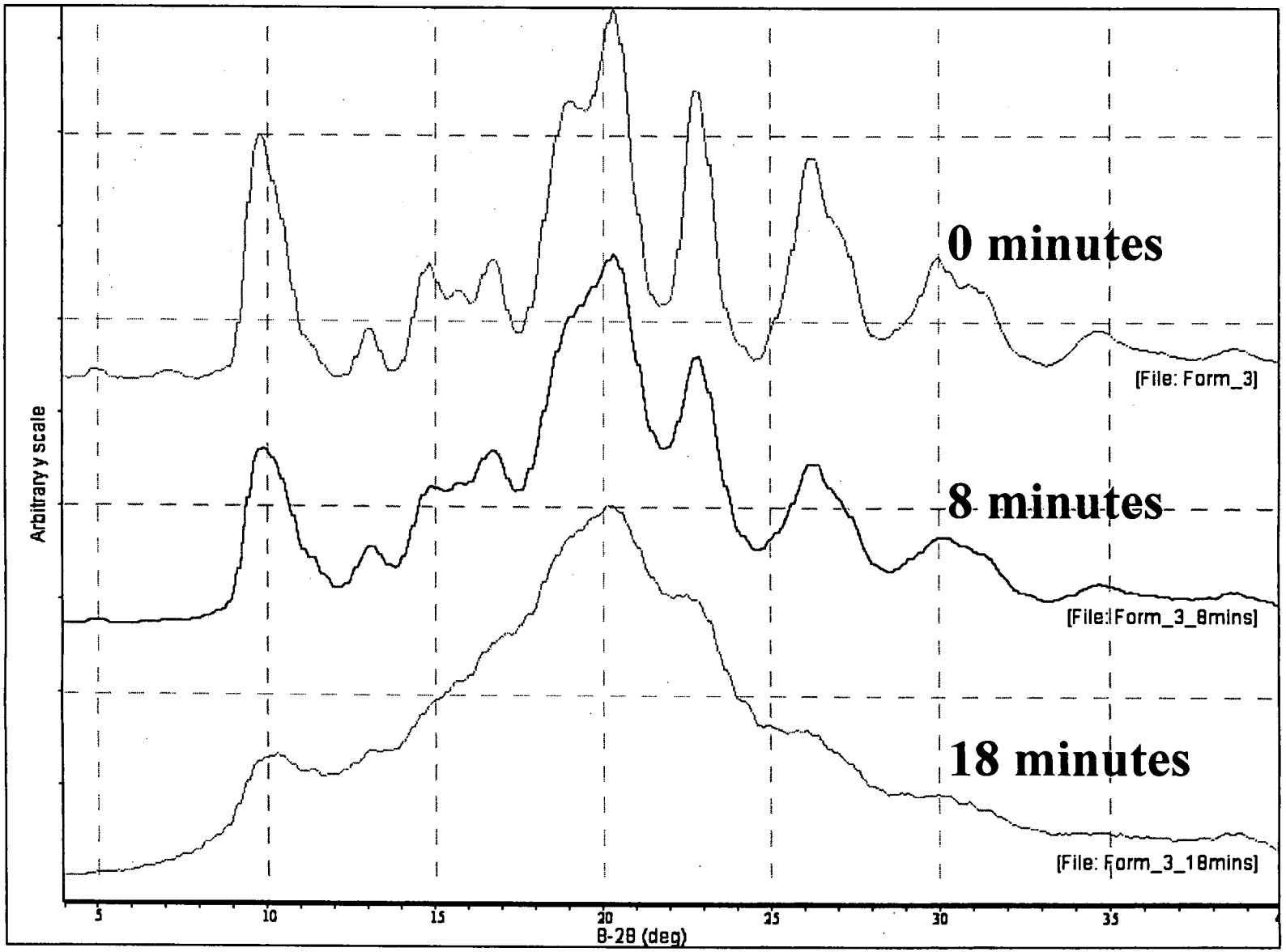
XRPD Pattern Analysis: Cryo-Grinding of Alpha Form



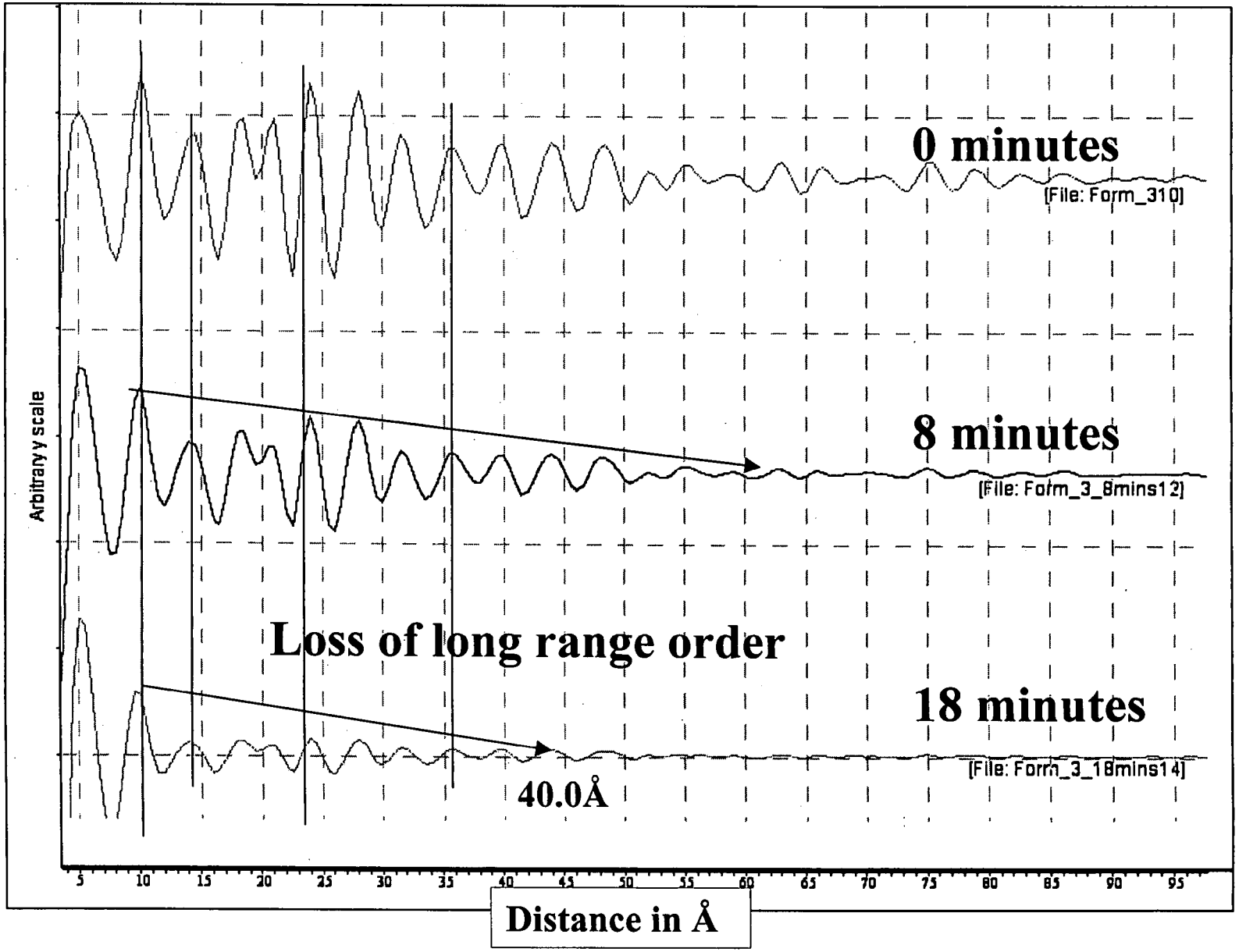
XRPD Pattern Analysis: PDF of Cryo-Ground Alpha Form



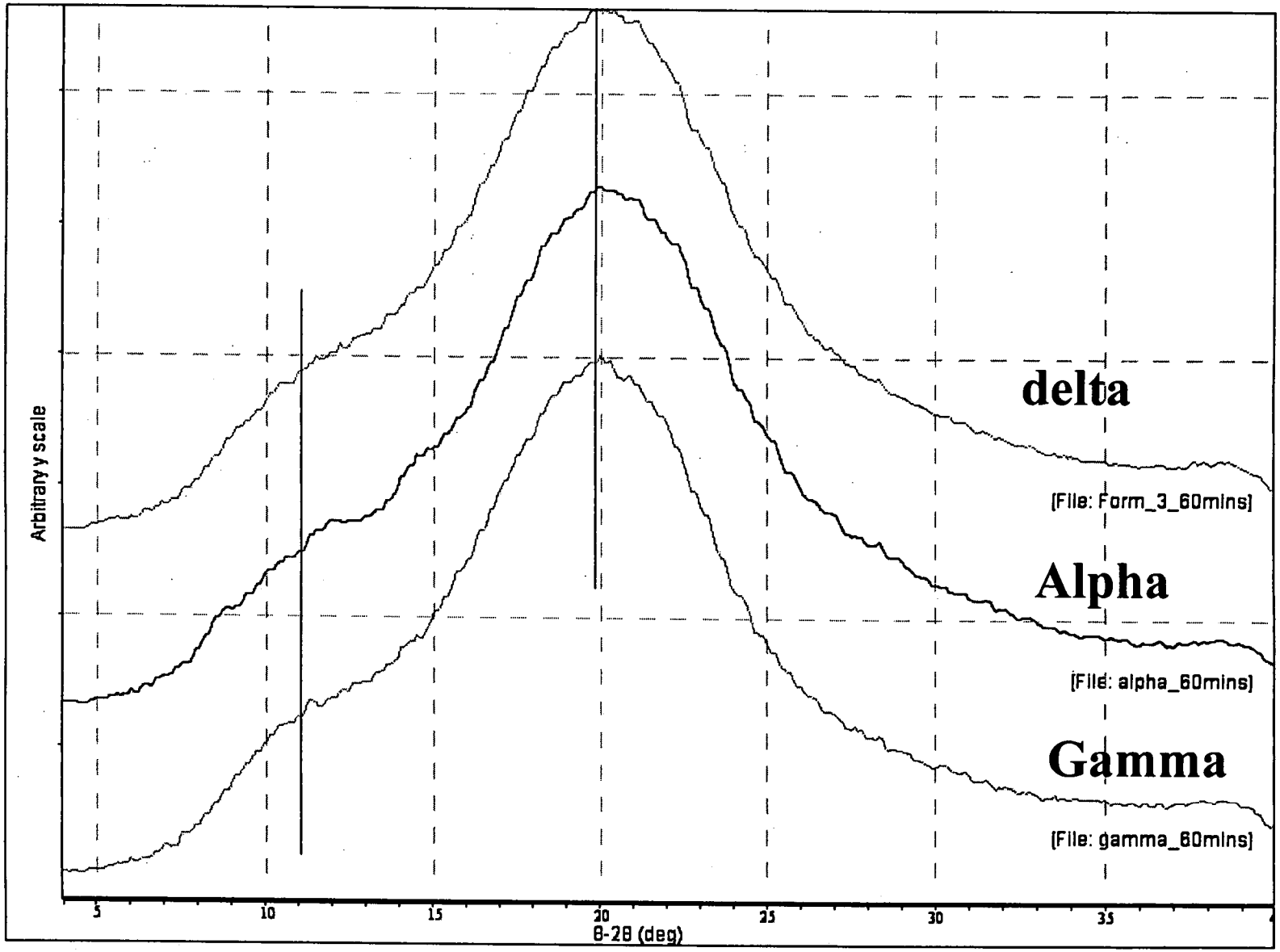
XRPD Pattern Analysis: Cryo-Grinding of Form delta



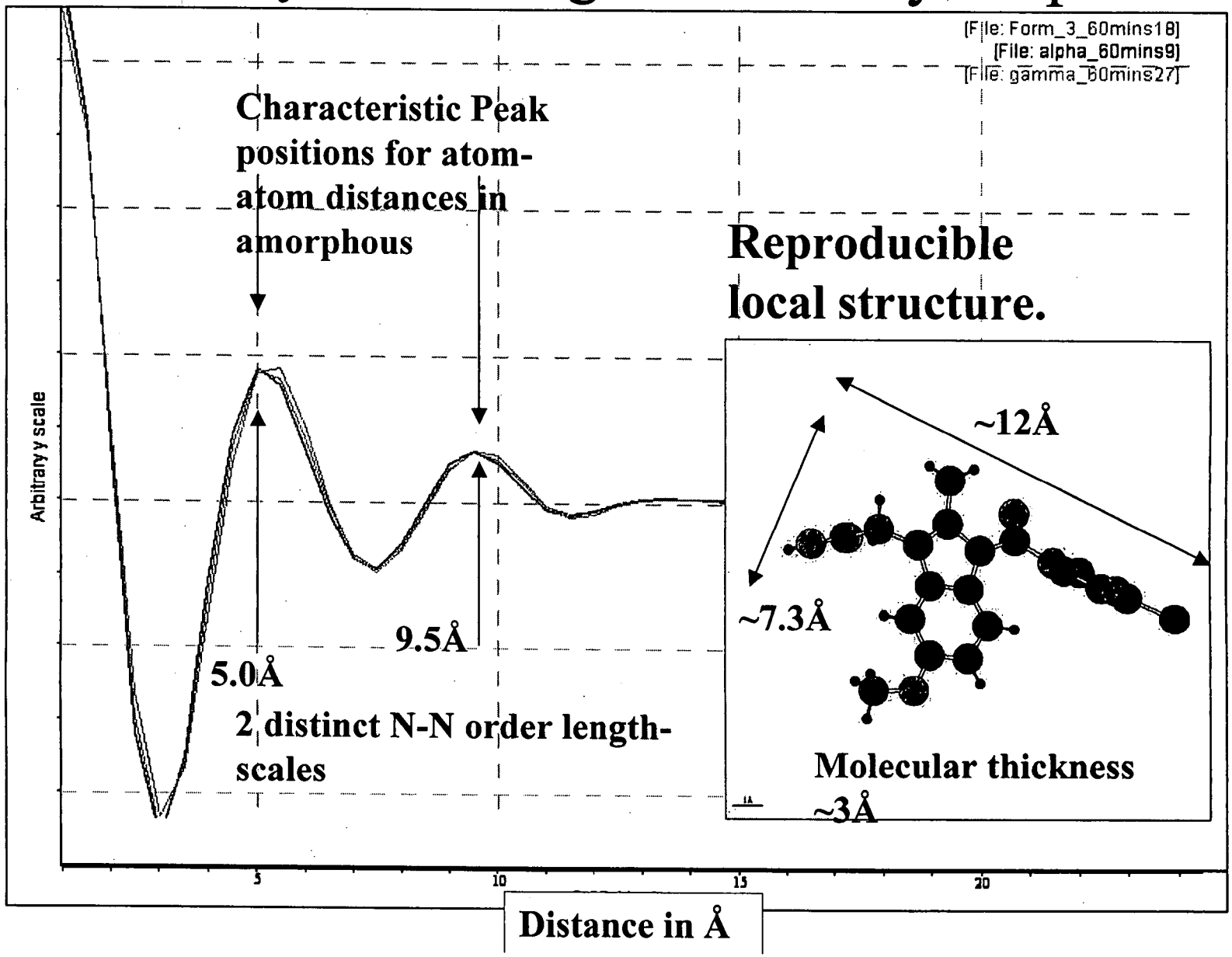
XRPD Pattern Analysis: PDF of Cryo-Ground Form delta



XRPD Pattern Analysis: 60 minutes Cryo-Grinding of all 3 Forms



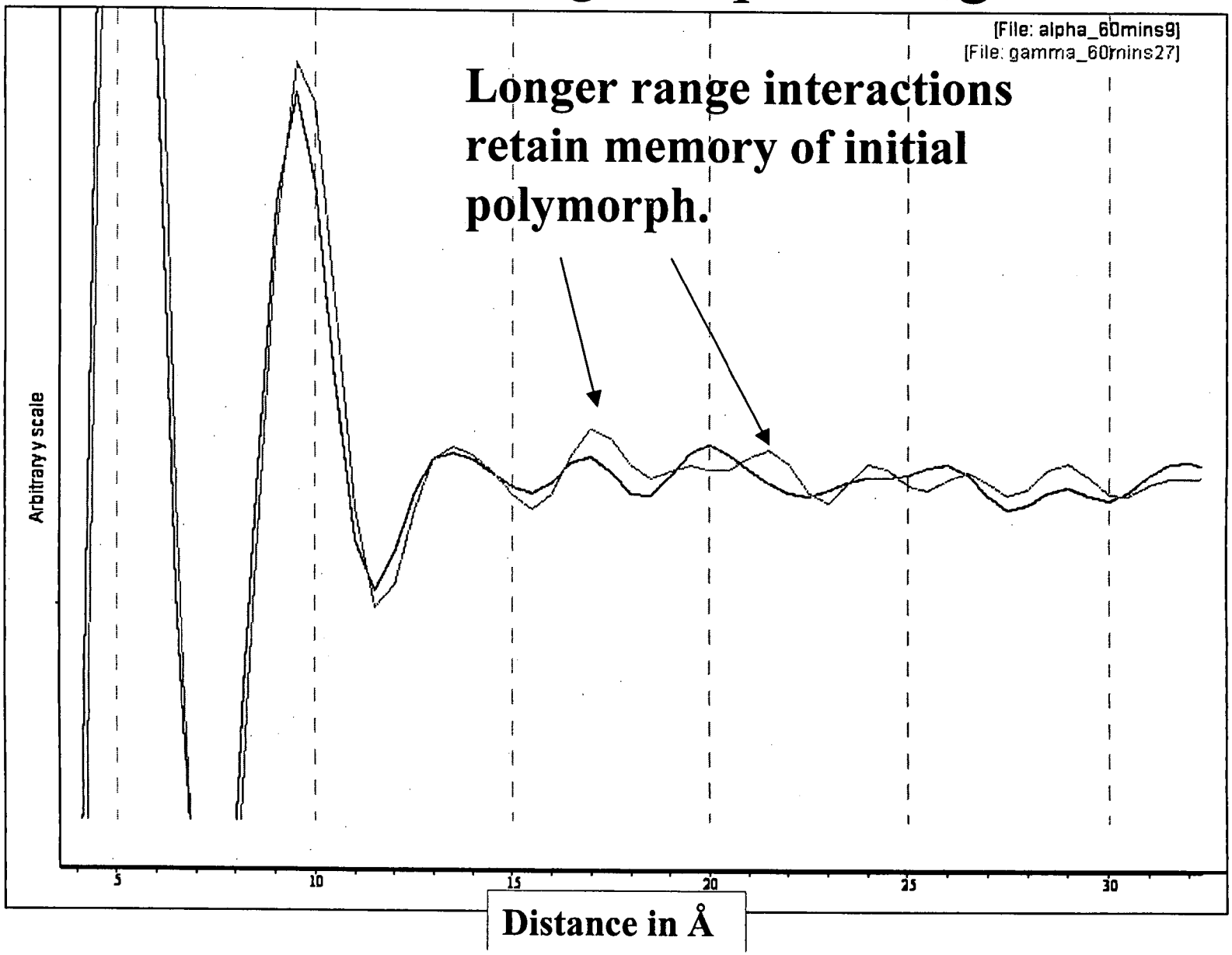
XRPD Pattern Analysis: PDF's for 60 minutes Cryo-Grinding of all 3 Polymorphs



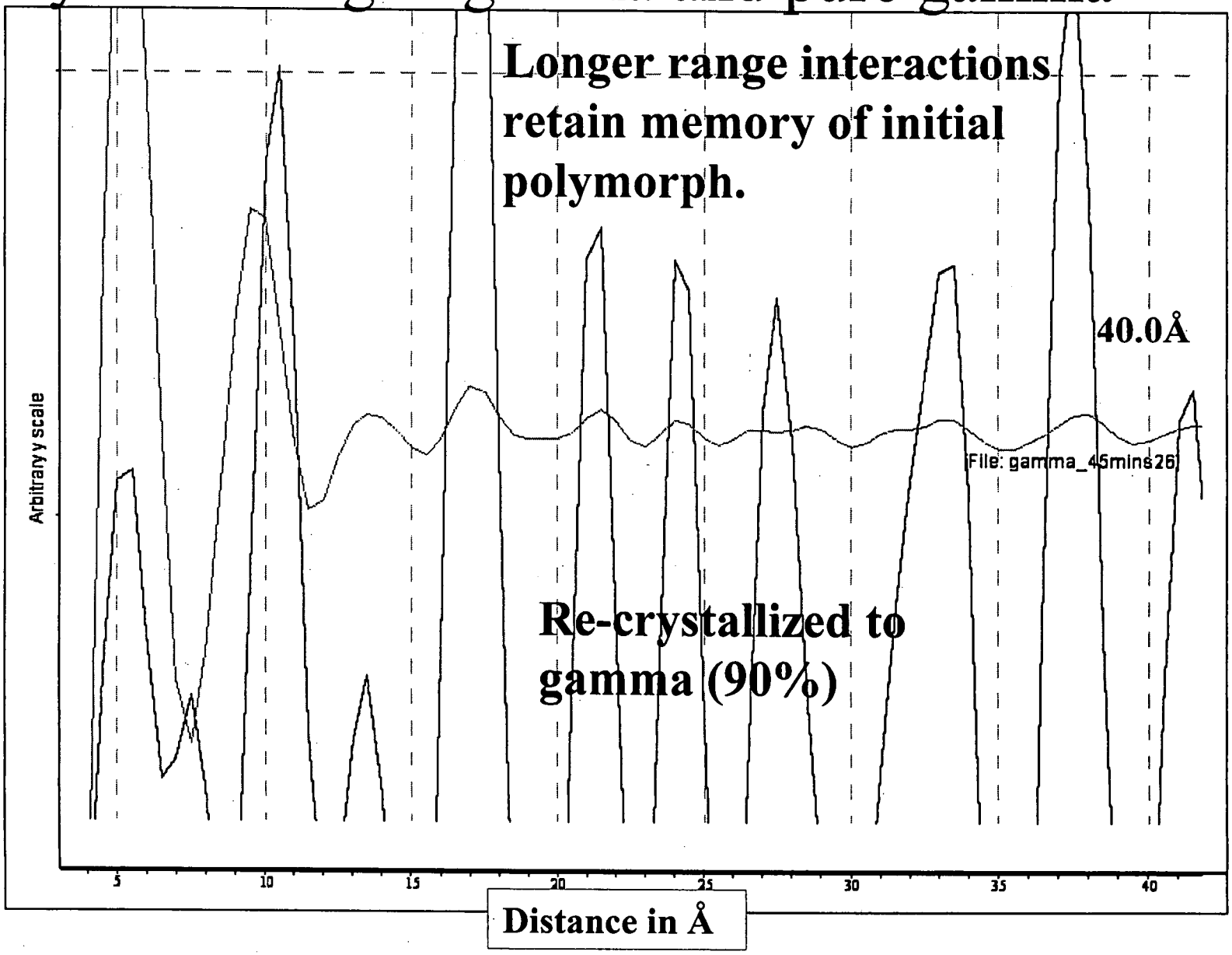
Nature of Amorphous Form

- Cryo-Grinding crystalline IMC produced a common amorphous form.
  - Amorphous Form characterized by two N-N order length-scales of ~5.0Å and ~9.3Å.
  - Different N-N length scales appear within a random connected network through covalent bonding and molecular anisotropy.
  - Not a "true amorphous" phase with isotropic N-N order (like ionic systems.)
  - Thermodynamically relatively stable

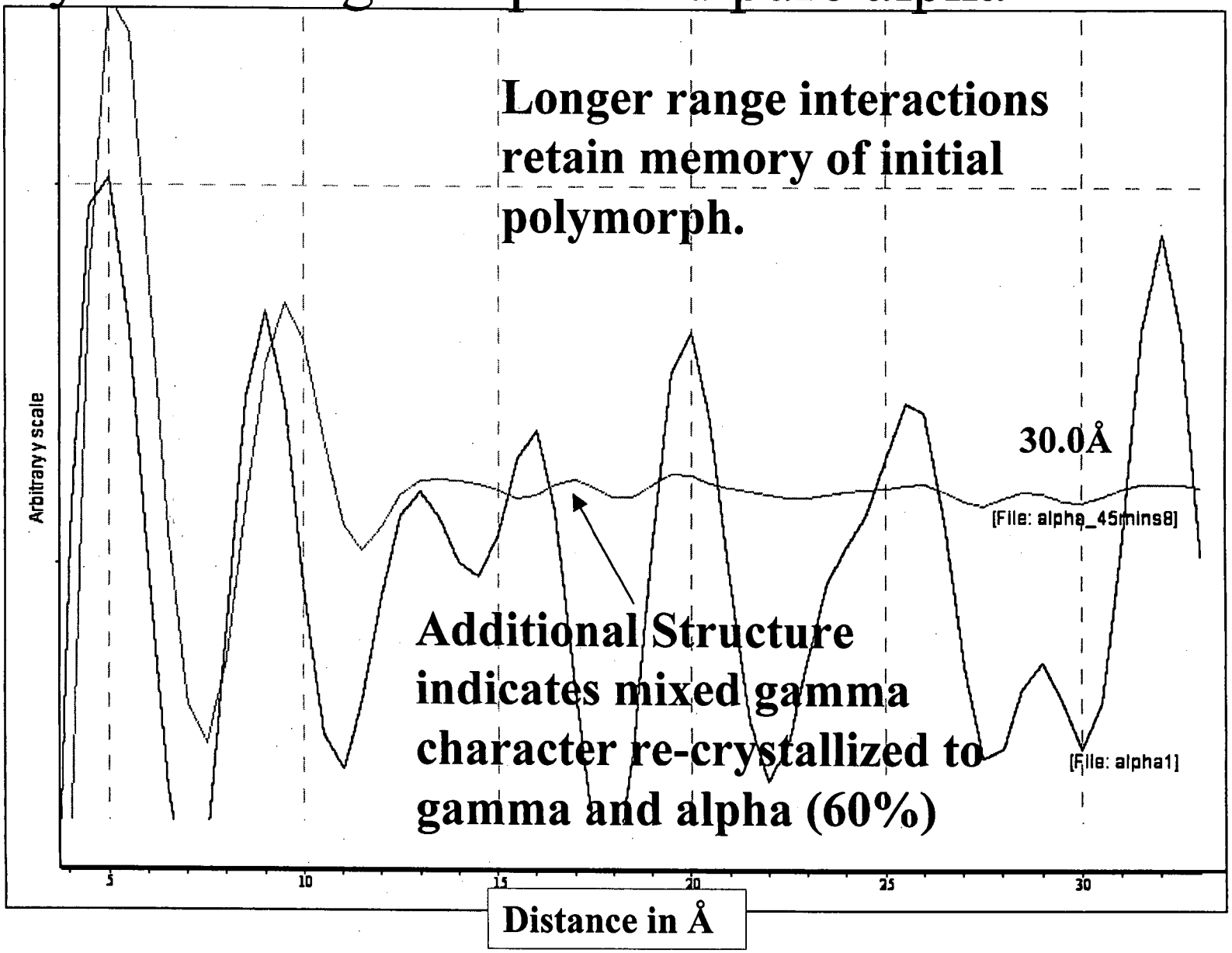
XRPD Pattern Analysis: PDF's for 60 minutes Cryo-Grinding of alpha and gamma



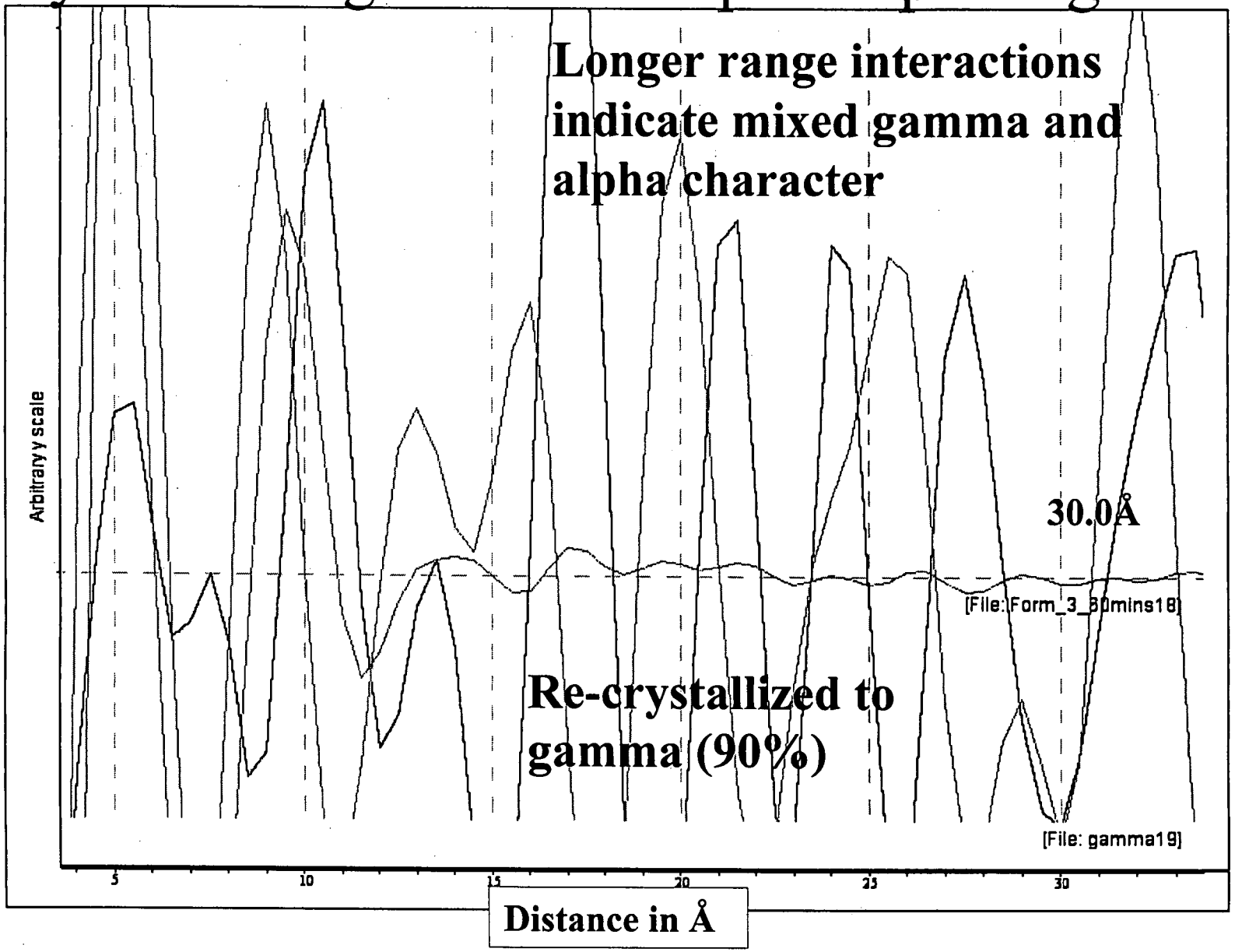
XRPD Pattern Analysis: PDF's for 60 minutes Cryo-Grinding of gamma and pure gamma



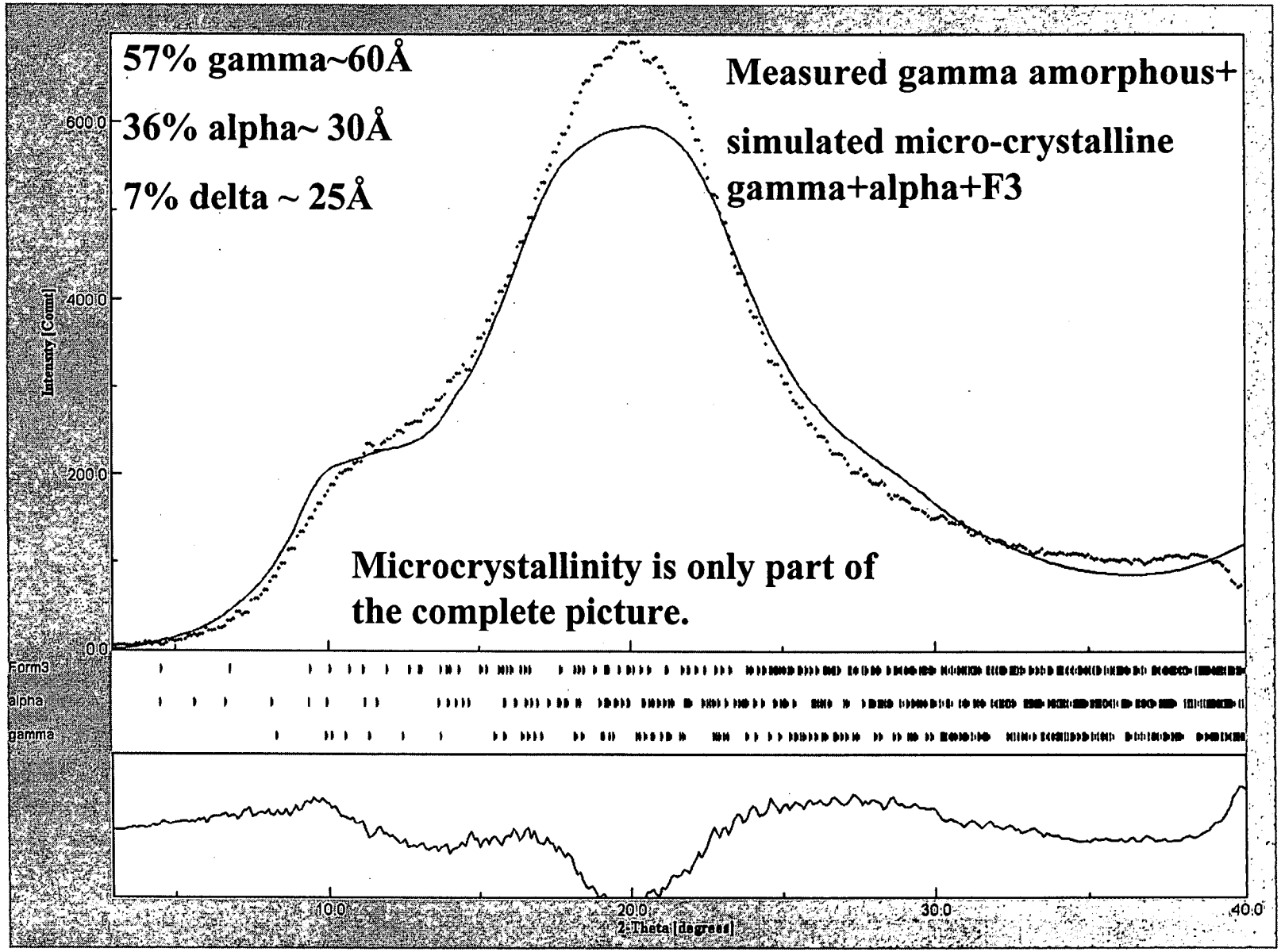
XRPD Pattern Analysis: PDF's for 60 minutes Cryo-Grinding of alpha and pure alpha



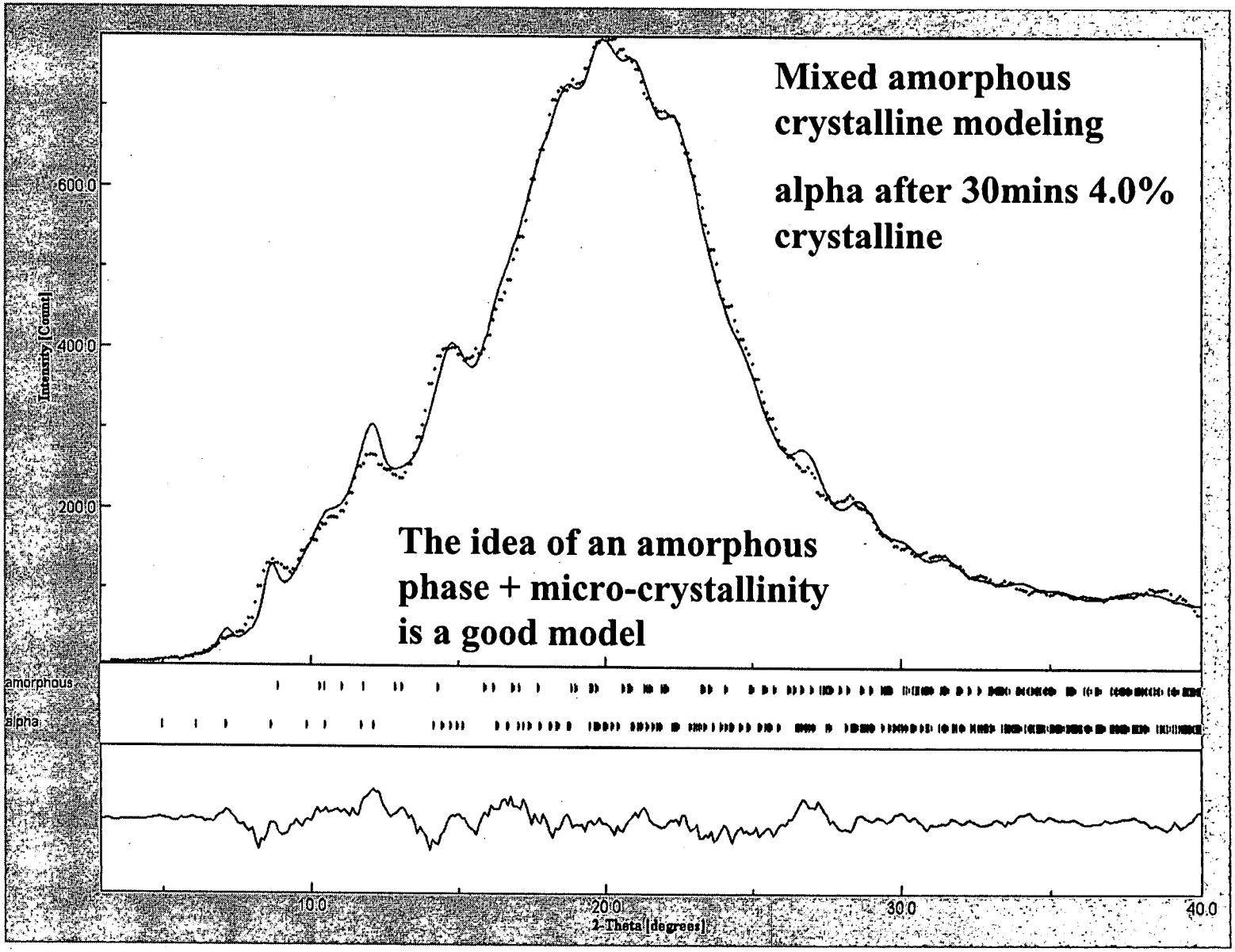
XRPD Pattern Analysis: PDF's for 60 minutes Cryo-Grinding of delta and pure alpha + gamma



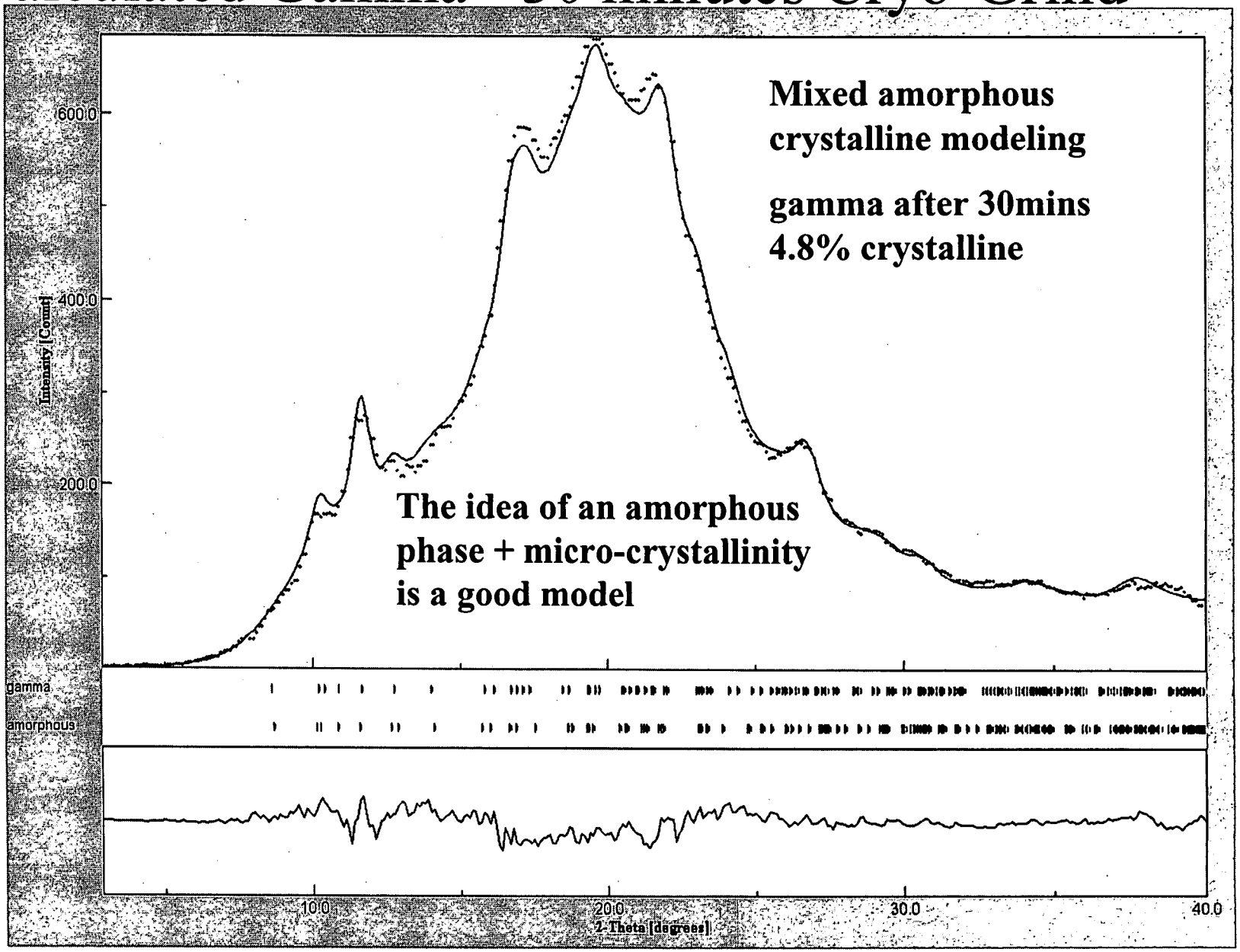
XRPD Pattern Analysis: Measured + Calculated Alpha - 60 minutes Cryo-Grind



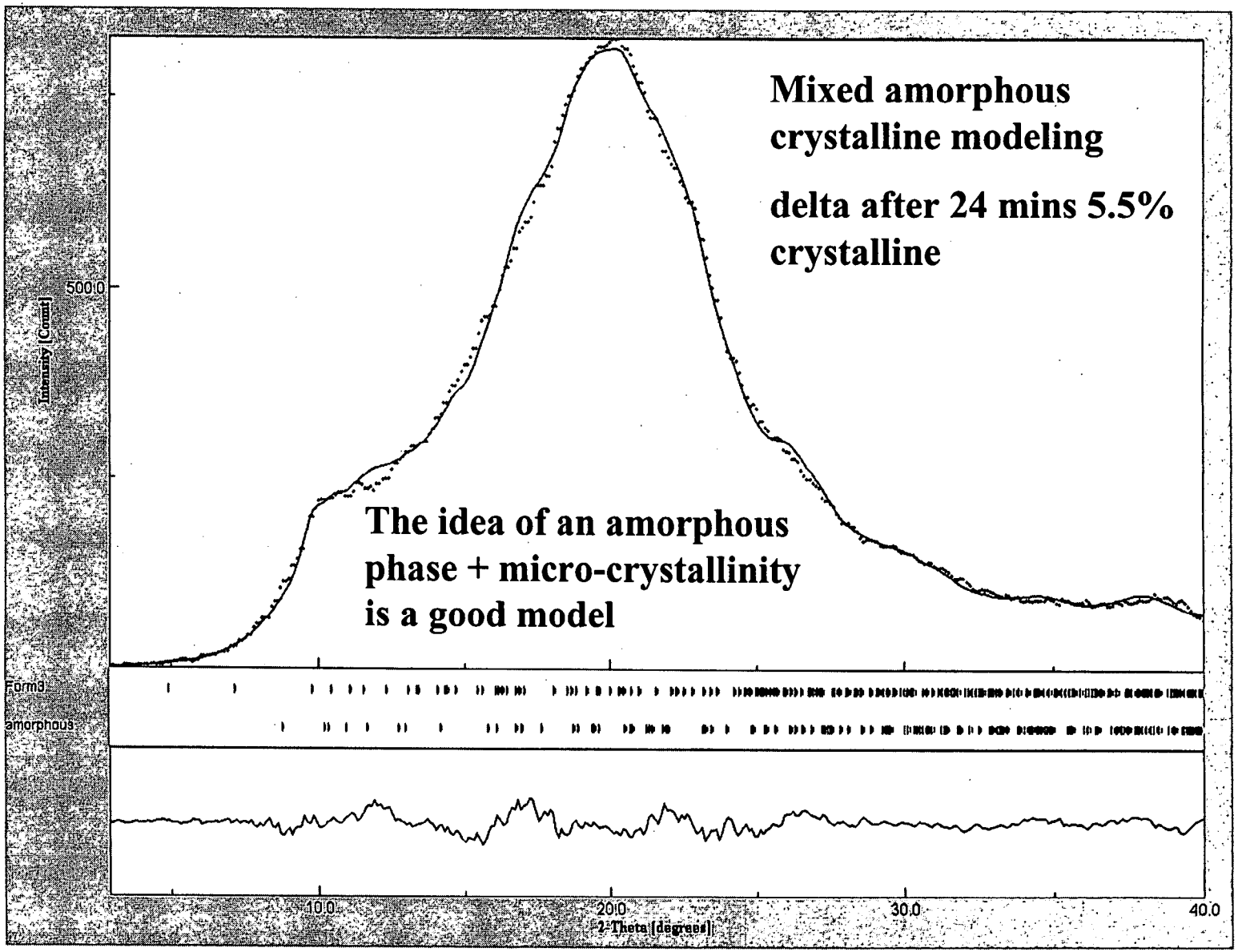
XRPD Pattern Analysis: Measured + Calculated Alpha - 30 minutes Cryo-Grind



XRPD Pattern Analysis: Measured + Calculated Gamma - 30 minutes Cryo-Grind

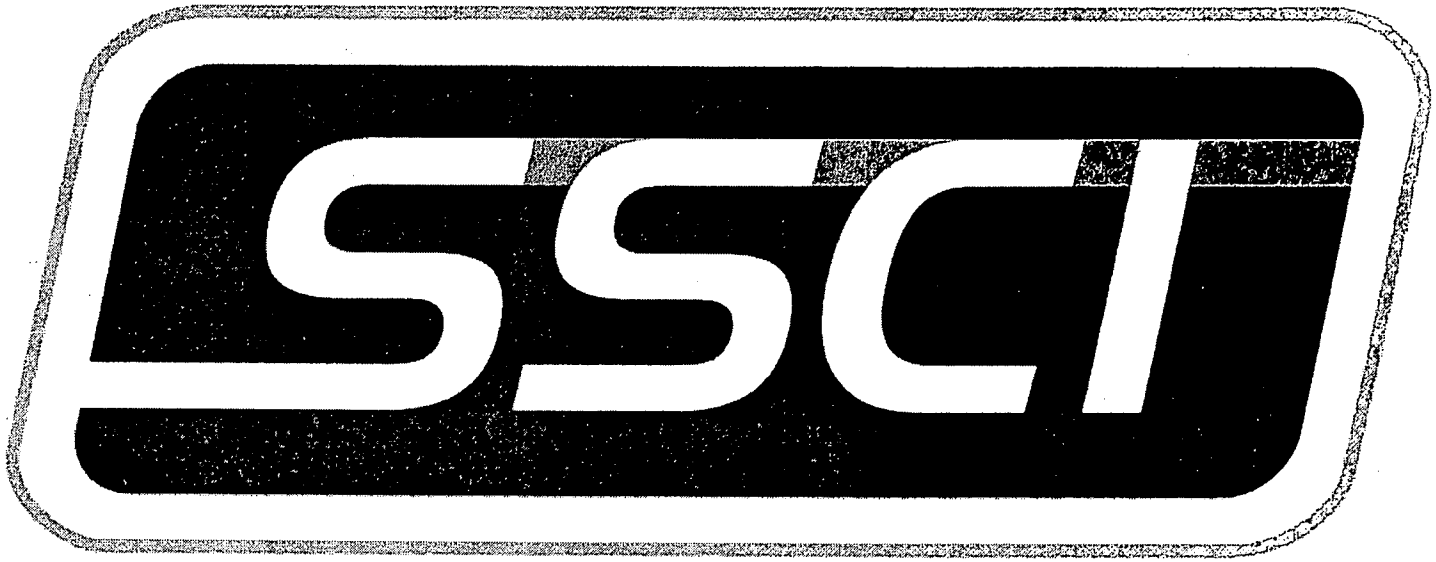


XRPD Pattern Analysis: Measured + Calculated delta - 30 minutes Cryo-Grind



Cryo-Grinding of Crystalline Material to give Amorphous Material

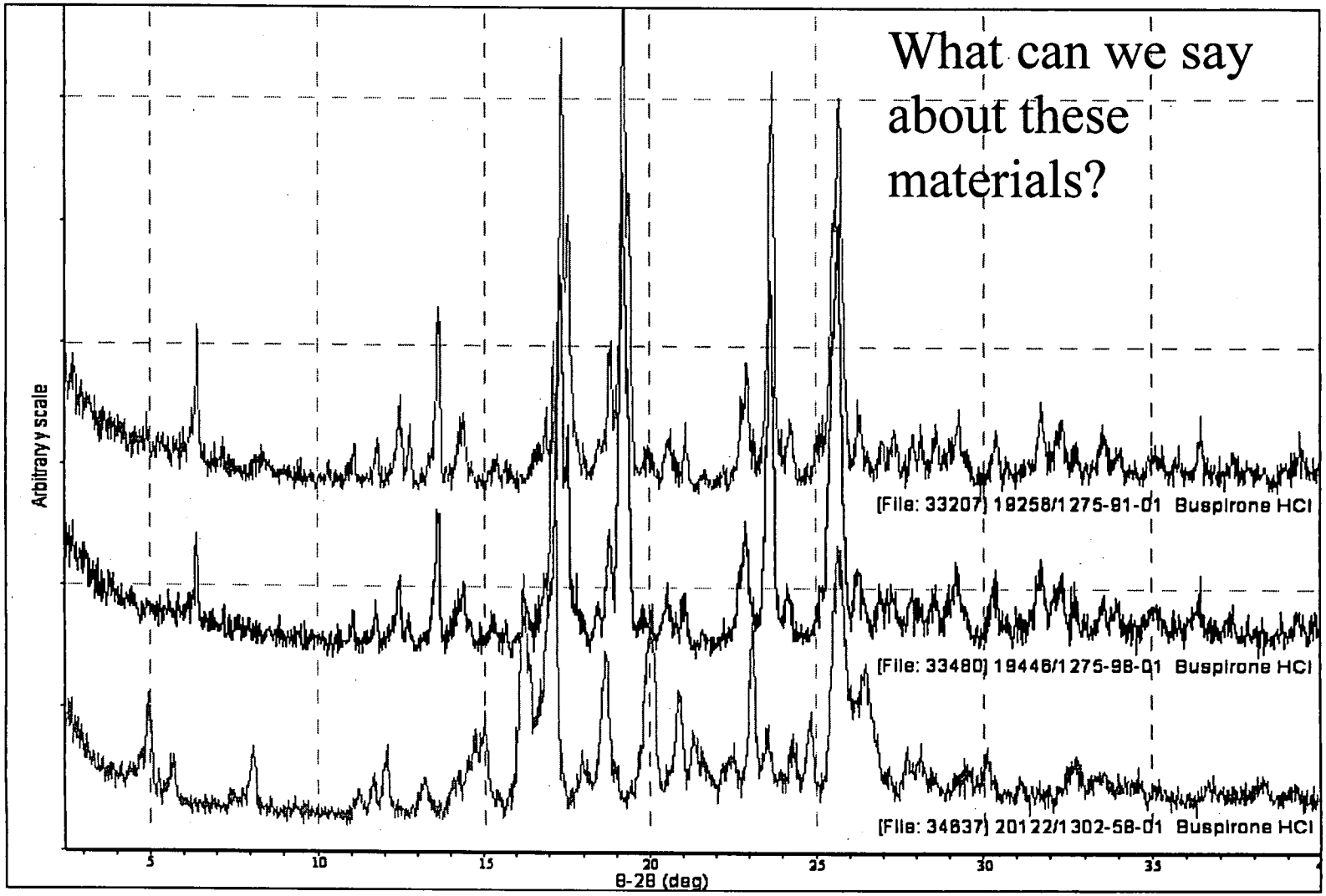
- Cryo-Grinding crystalline IMC material gives common amorphous phase + remnant micro-crystallinity.
  - Amorphous phase consists of 2 order length-scales corresponding to N-N molecular order.
  - The starting polymorph molecular packing is 'remembered' in the amorphous form.
  - Evidence of mixed longer range molecular order for alpha and delta polymorphs.
  - Origin of different physical properties for amorphous forms depending on work history.



XRPD Pattern Analysis:

From Matching to Molecular Imaging

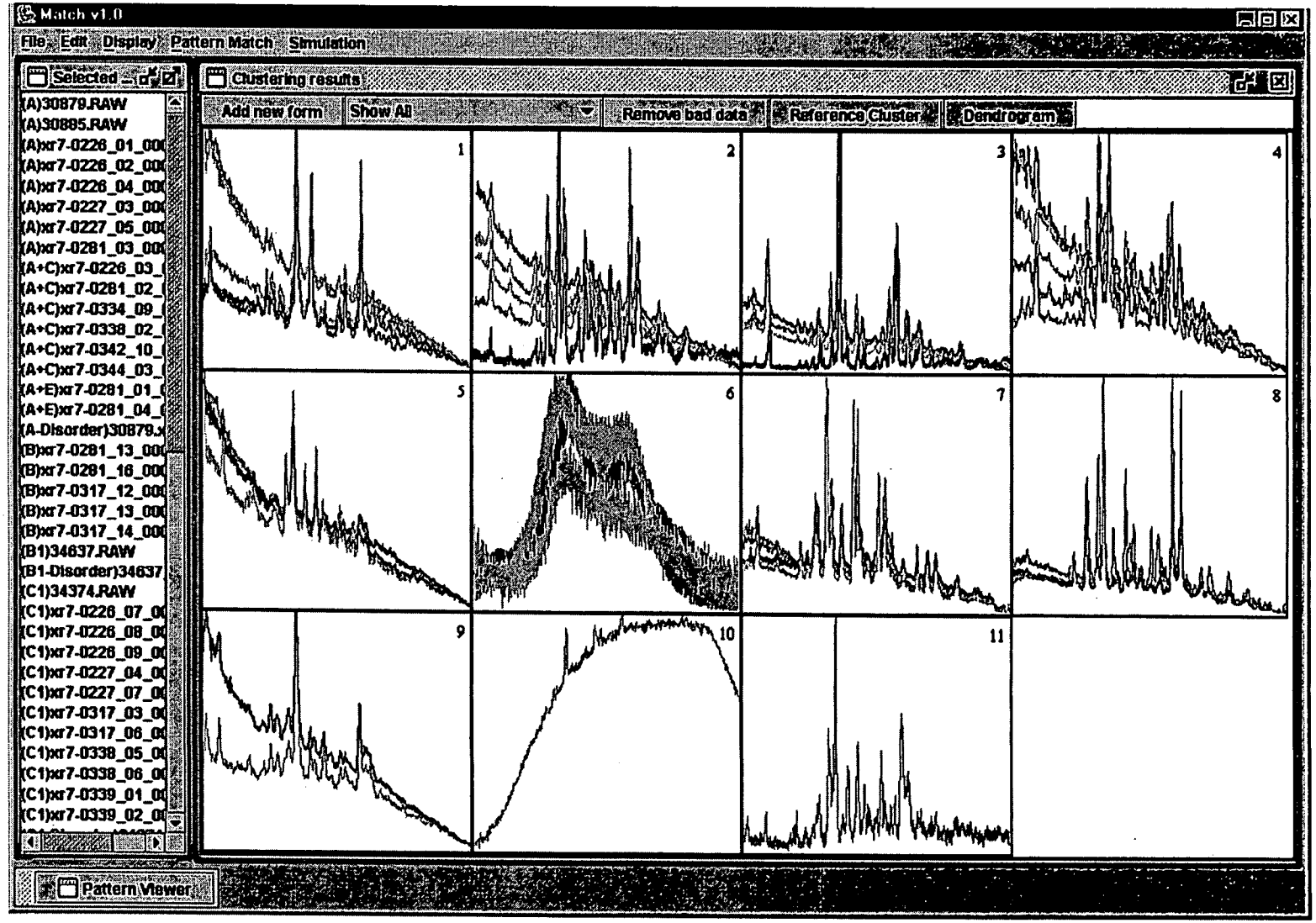
XRPD Patterns



XRPD Pattern Analysis

- Traditional Analysis - Pattern Matching
  - Sameness; Mixtures; New Forms
- Direct Electron Density Imaging
  - Small-Medium Molecules imaged
- Pair-Wise Distribution Function Analysis
  - Disorder - Order relationships
  - Deconstruction of Molecular Building Blocks.

Traditional XRPD Pattern Analysis

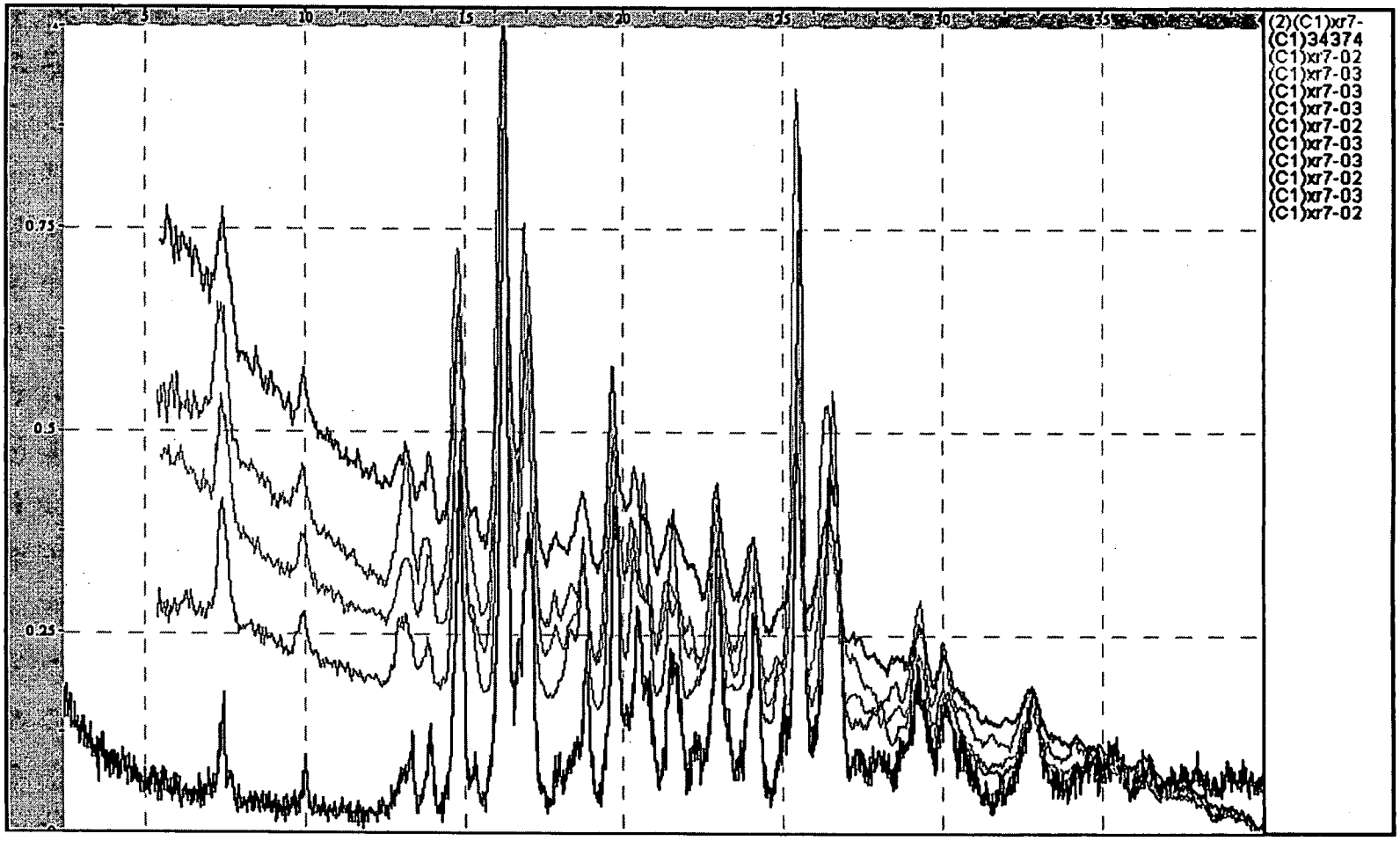


Matching for Sameness - Mixtures - New Forms

Traditional XRPD Pattern Analysis

- Pattern Matching Based Upon HCA using novel metrics for sameness.
  - Peak Position + Probability
    - Mixtures
    - Sameness
  - General Intensity Envelope
    - Disorder - Order
    - Sameness
- Limited information on nature of new forms

Measure of Sameness



Robust sameness metric independent of widely varying data quality

XRPD Pattern Analysis: The Next Step - 1.) Direct Electron Density Imaging

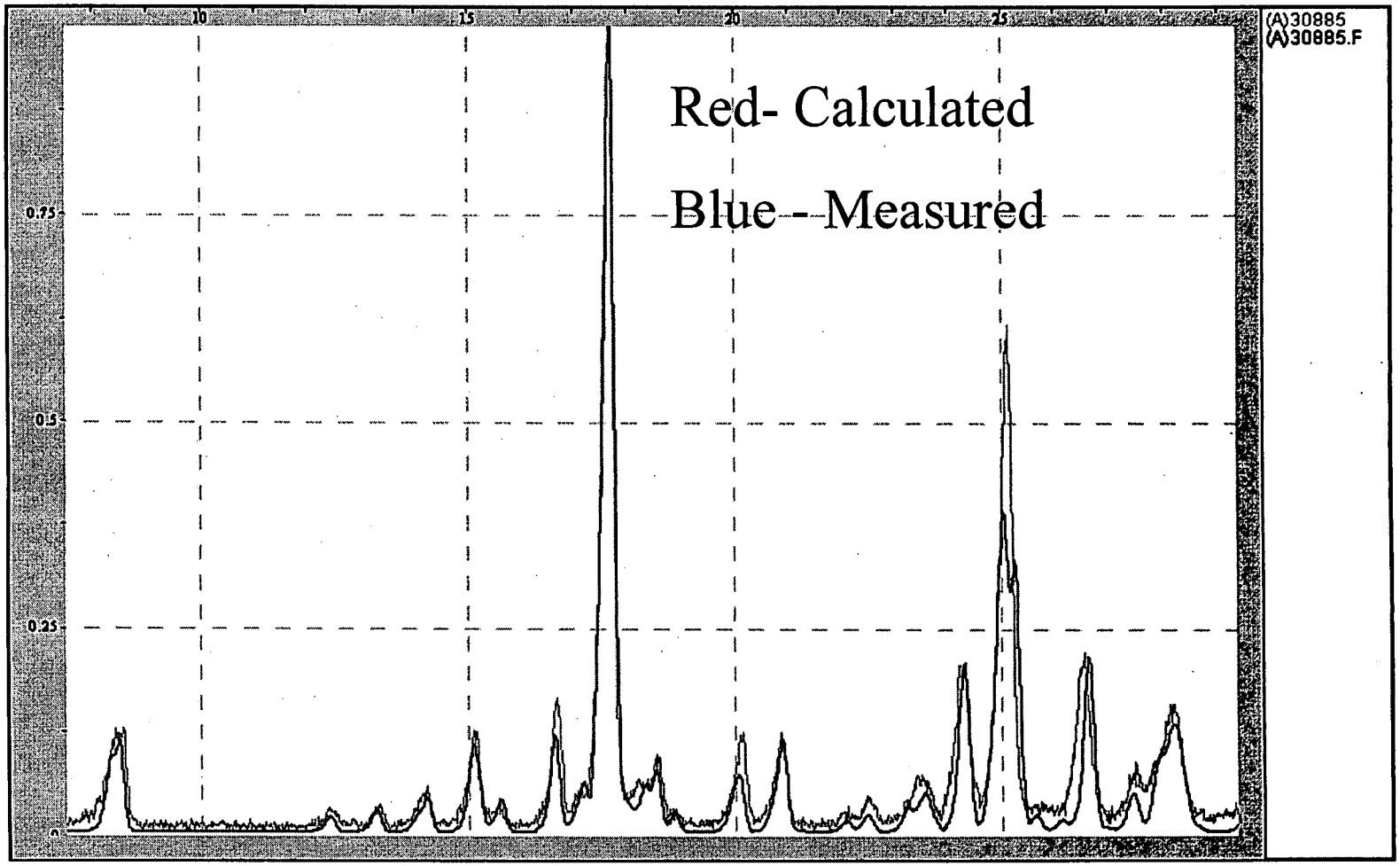
- A 3D image of Electron Density, requires a 3D decomposition of the XRPD data.
  - Distribution of measured x-ray intensity over 3D reciprocal lattice.
    - Indexing
    - Allocation of Space Group
    - Extraction of Reduced Structure Factors
- Calculate ED distribution
  - Reduce to 3D node distribution

XRPD Pattern Analysis: Indexing

XRPD Pattern Analysis: Indexing

- Reverse Monte Carlo Methods used to search limited phase space
  - Phase space limited to contain only realistic solutions allowed by molecular packing.
  - Global solution optimization once close to a possible solution.
  - Search for at least 5 distinct solutions.
- Index Solutions used to increase reliability of Pattern Matching

XRPD Pattern Analysis: Extraction of Reduced Structure Factors



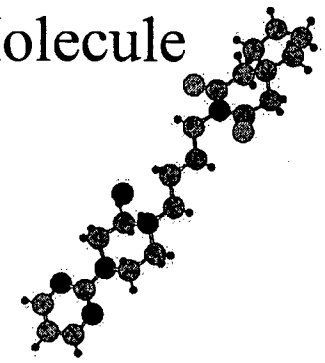
XRPD Pattern Analysis: Extraction of Reduced Structure Factors

- Le-Bail and Pawley Refinements used to extract reduced structure factors.
  - Goodness of Fit between calculated and measured patterns used to establish best index solution.
  - Reduced Structure Factors equivalent to Single Crystal Data
    - 3D distribution of x-ray intensity in reciprocal space.

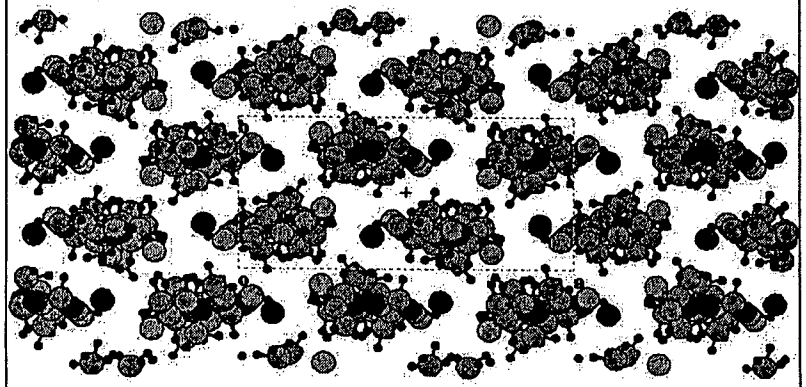
XRPD Pattern Analysis: Direct Visualization of Electron Density

Form A

Original Molecule

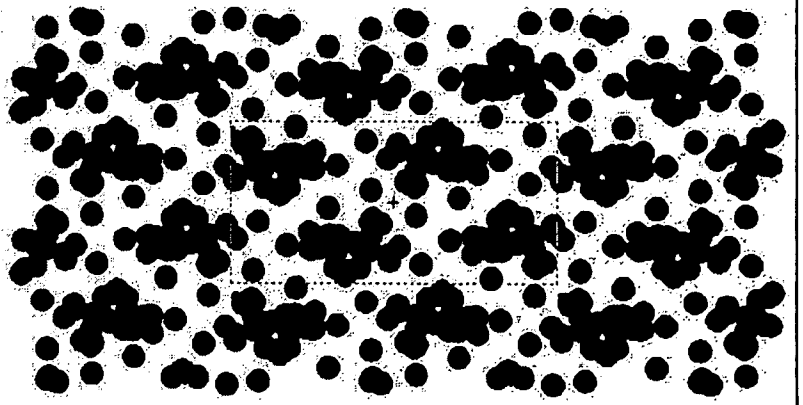


Single crystal structure



1Å

Electron Density Imaging

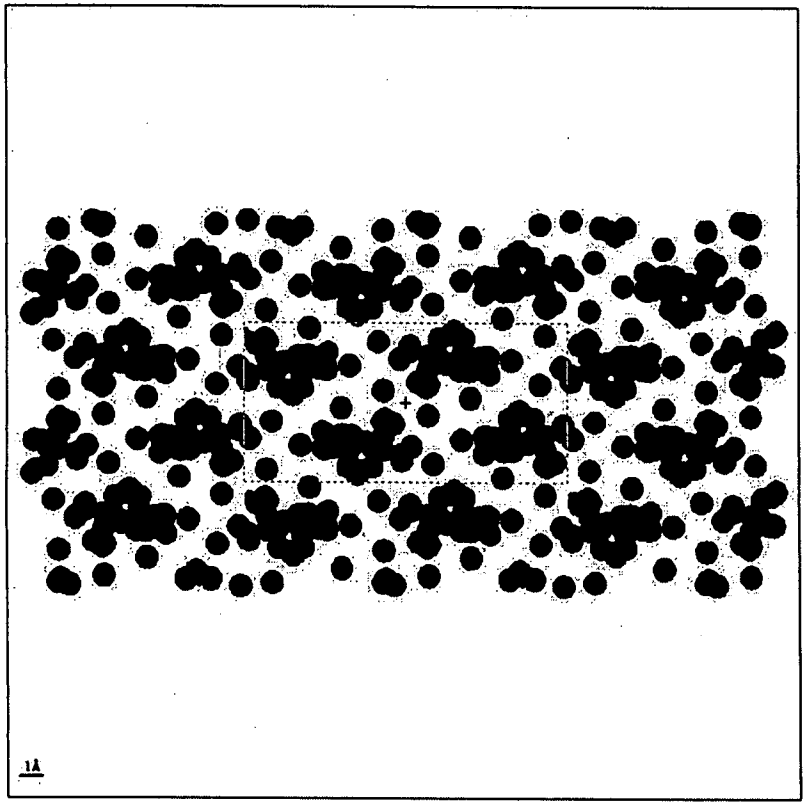


1Å

XRPD Pattern Analysis: Direct Visualization of Electron Density

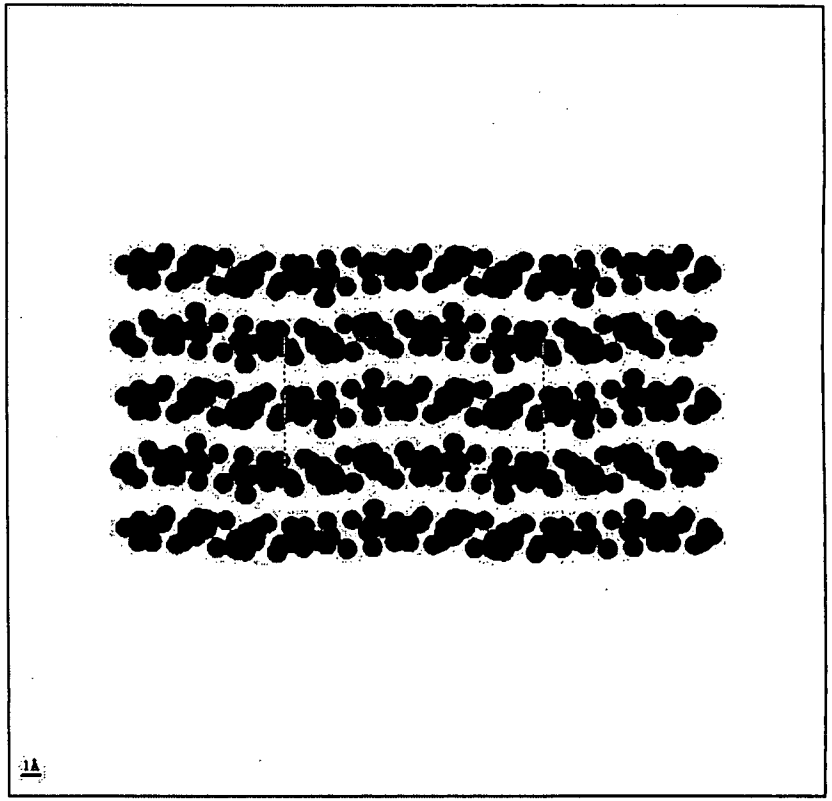
Form A P21/n

a=14.663 b=7.084 c=21.529
beta=103.507 volume=2175

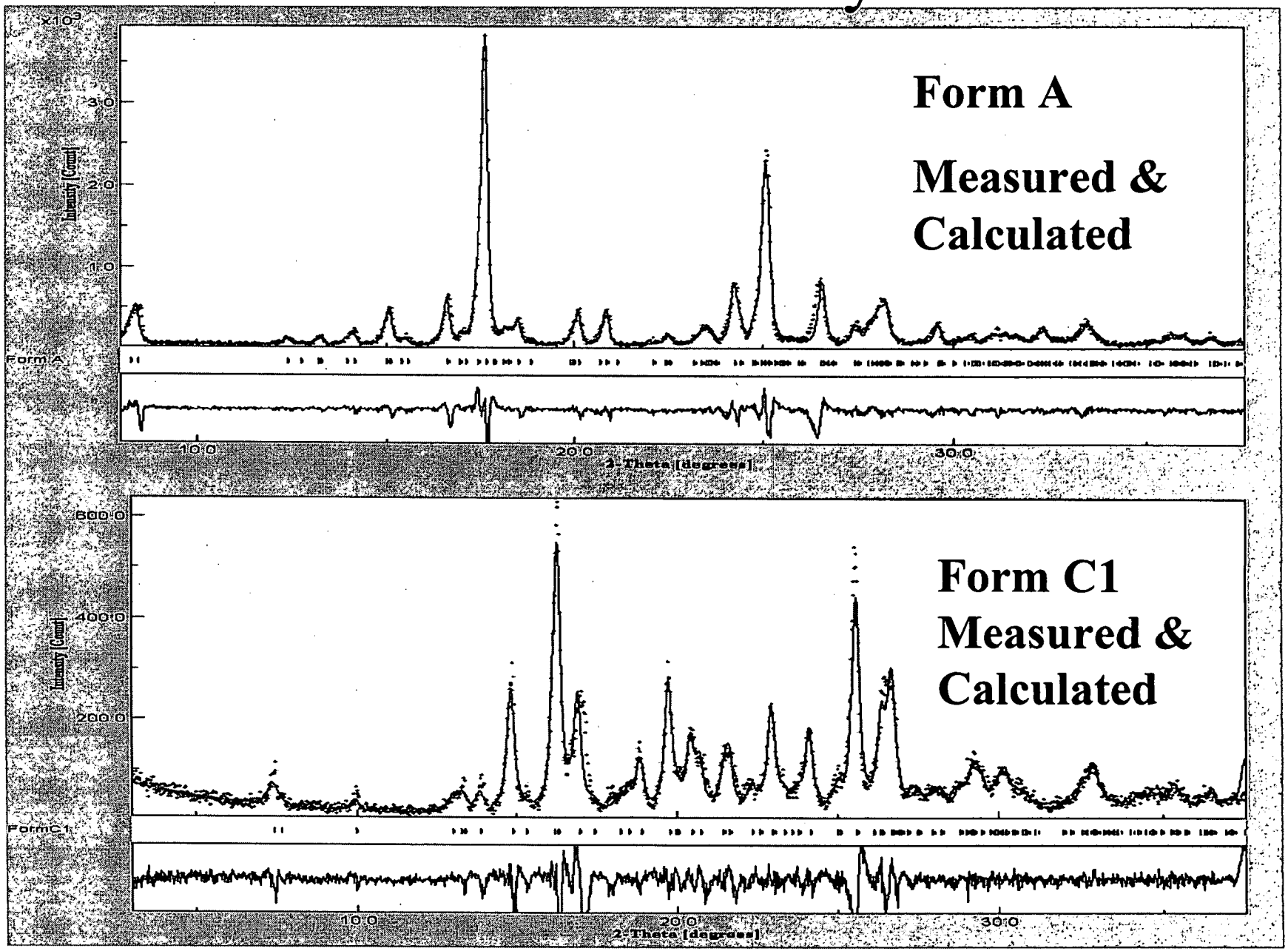


Form C1 P212121

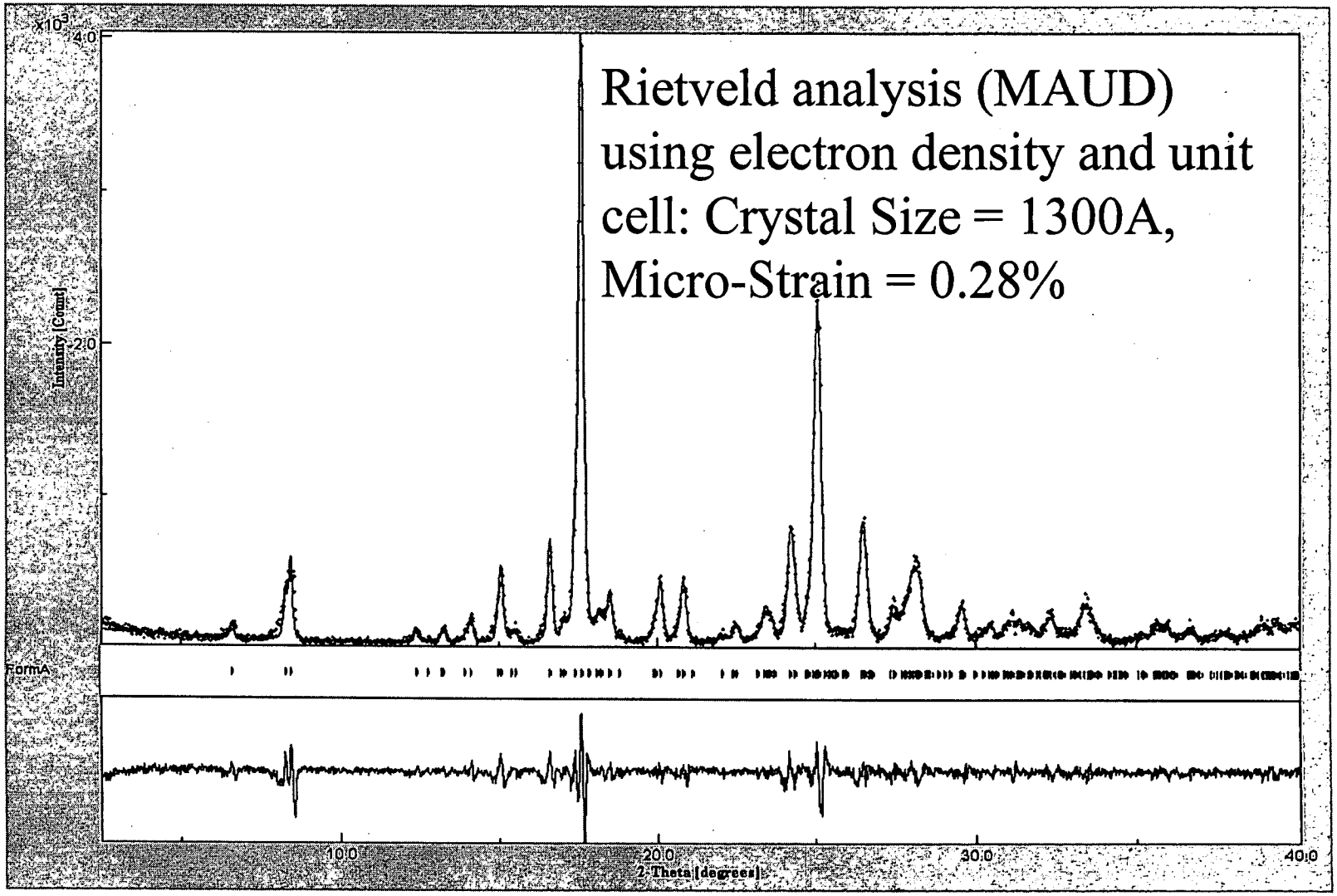
a=13.252 b=6.956 c=23.866
volume=2200



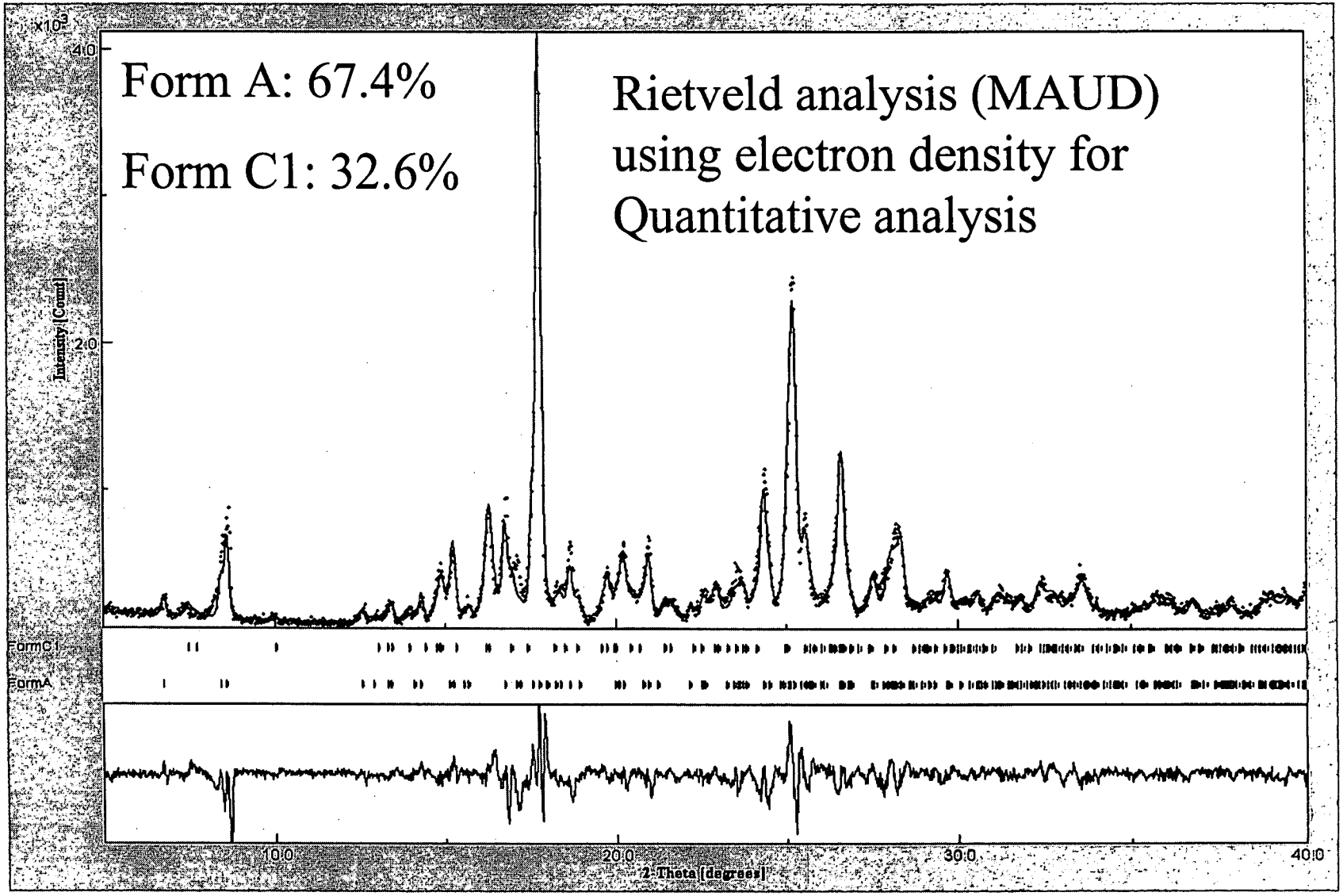
XRPD Pattern Analysis:



XRPD Pattern Analysis - Use of Electron Density map for Rietveld



XRPD Pattern Analysis - Use of Electron Density map for Rietveld



XRPD Pattern Analysis: Direct Visualization of Electron Density

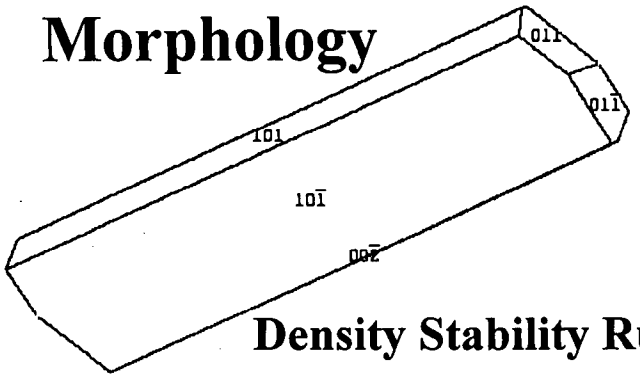
- Electron Density Model Allows accurate prediction of materials properties:
  - True Density -> Thermodynamic Stability
  - Morphology + Morphology engineering
  - Presence of gross physical features
    - Channels
    - Tunnels
  - Prediction of manufacturability

XRPD Pattern Analysis: Direct Visualization of Electron Density

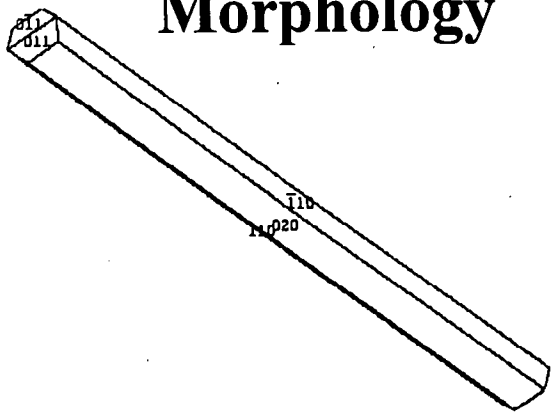
- Small/Medium molecules with < 20 atoms (non H) in asymmetric unit easy to visualize.
  - Each atom requires 5 -> 10 x-ray peak intensities to fully locate position.
  - Measurement range 2.0 -> 40.0 2Theta typically contains 60 -> 120 x-ray peak intensities.
  - Fall off in XRPD intensity for molecular systems will always limit direct visualization.

XRD Pattern Analysis: Physical Properties Prediction

Form A Morphology



Form C1 Morphology



Density Stability Rule

Form A density = 1.19 g/cm^3

Form C1 density = 1.18 g/cm^3

Experimental Occurrence

Form A: 123 ; Form C1: 32

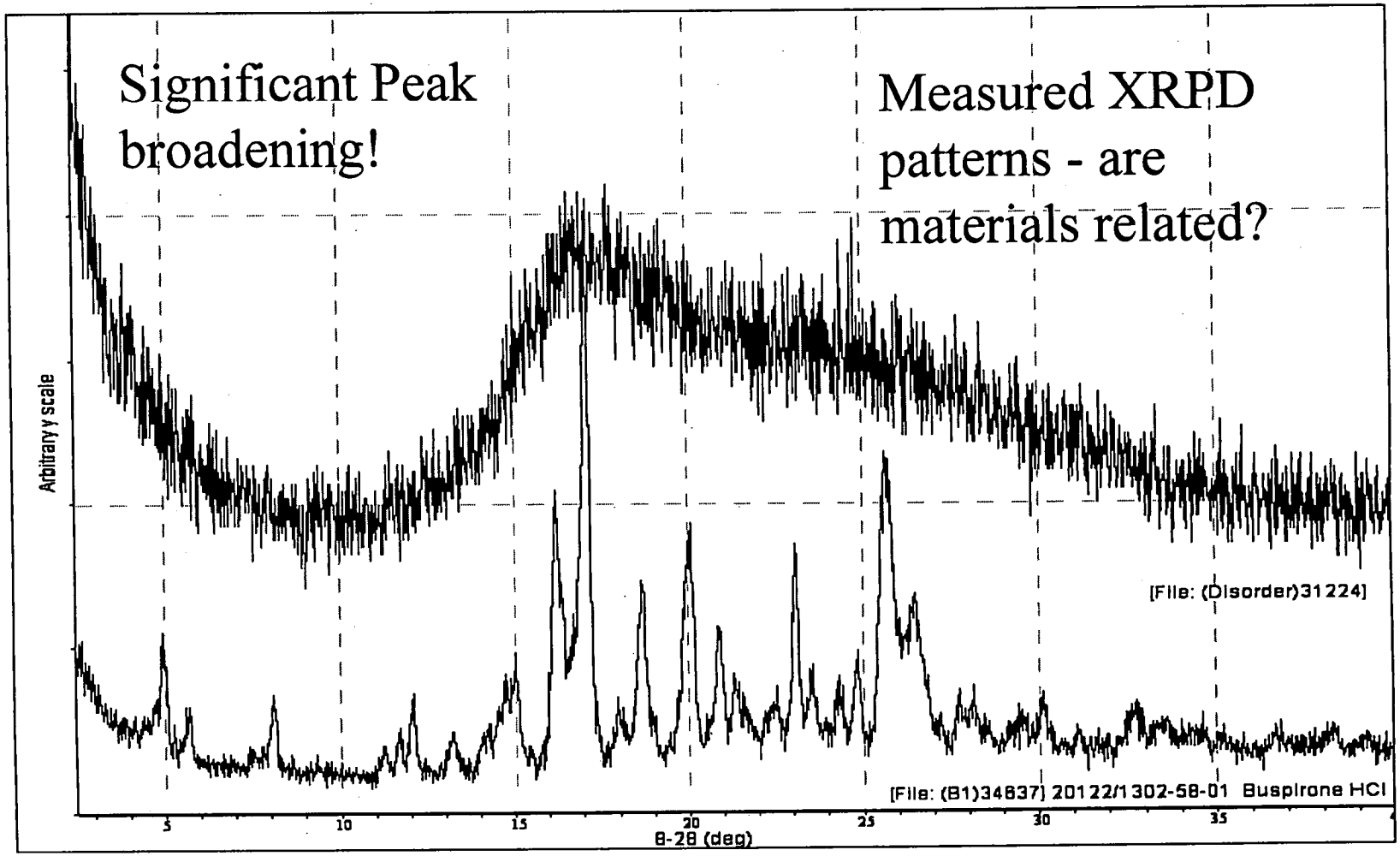
Inter-conversion: < 95° C: Form C1 >> Form A
Inter-conversion: > 95° C: Form A >> Form C1

Form C1 proved difficult to manufacture!

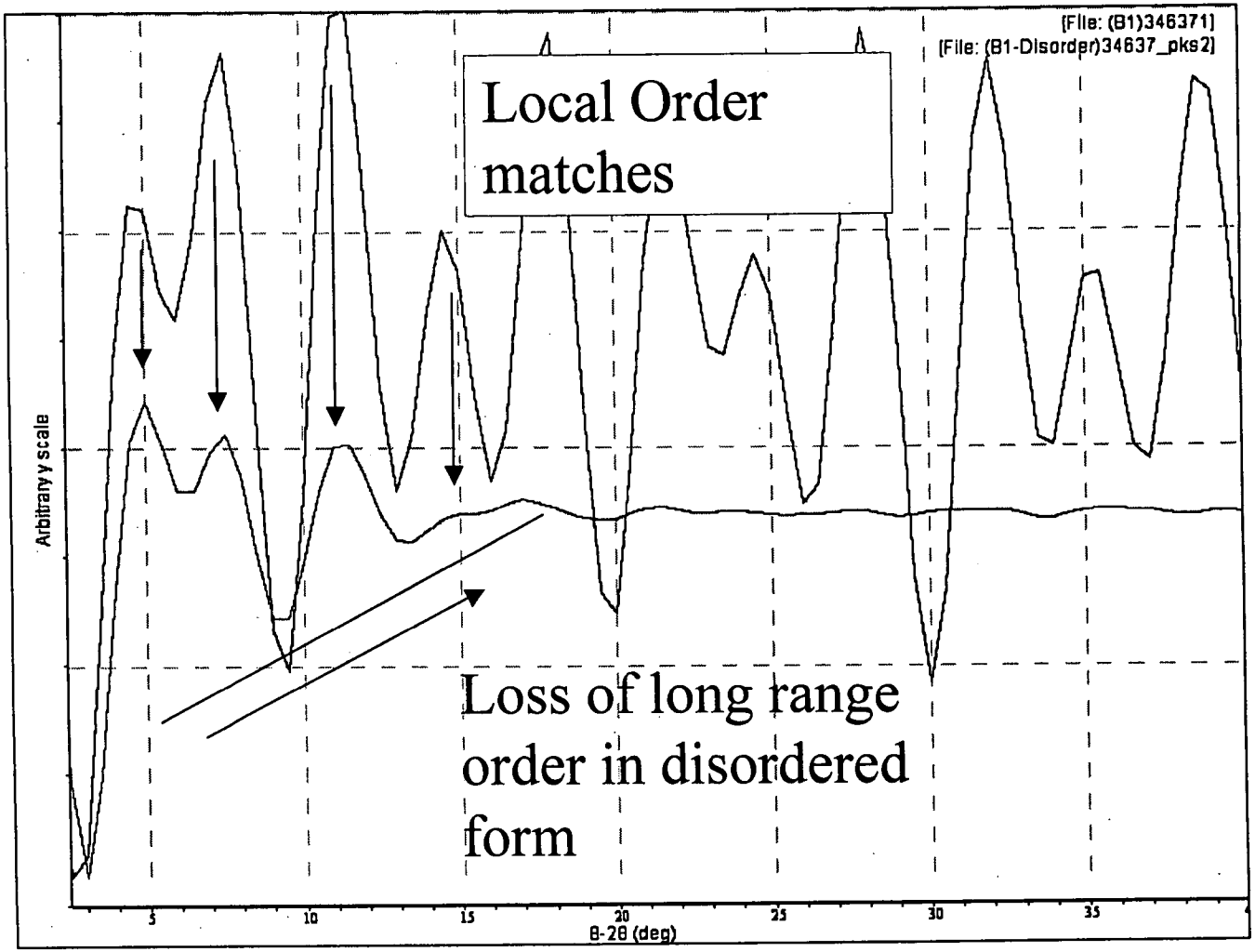
XRPD Pattern Analysis: The Next Step - 2.) Pair-Wise Distribution Functions

- Fourier Sine Transform of Reduced Structure Factors -> PDF.
  - Can be used on 1D or 3D diffraction data.
  - Used to isolate characteristic repeats and packing of atoms within solid forms.
  - Identify Order-Disorder relationships.
  - Break Down Complex Molecular Structures into Building Blocks.
- Improved Pattern Matching

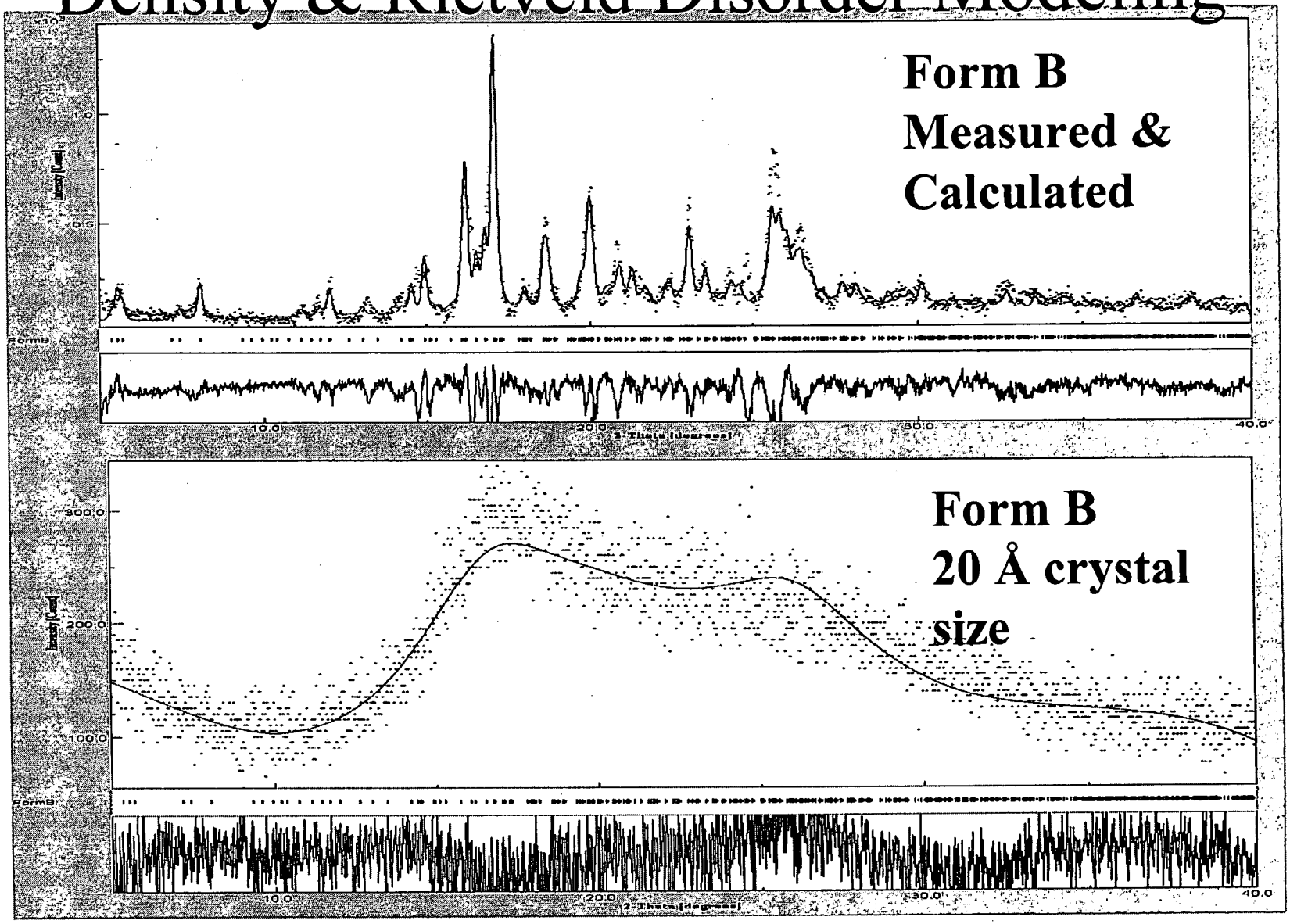
XRPD Pattern Analysis - PDF & Order - Disorder relationships



XRPD Pattern Analysis - PDF & Order - Disorder relationships



XRPD Pattern Analysis - Electron Density & Rietveld Disorder Modeling



Claims:

1. A method for distinguishing between different solid forms of two or more samples of a substance, which comprises

calculating a PDF for each of two or more solid samples, and

comparing the PDFs to determine whether the samples represent the same or different forms.

2. A method for determining whether an X-ray powder diffraction pattern of a first sample represents a disordered version of the same solid found in a second sample, which comprises

calculating a PDF for each of the samples, and

comparing the PDFs to determine whether the first sample represents a disordered version of the same solid found in the second sample.

3. A method of screening for new solid forms of a substance, which comprises

generating a plurality of solid samples of the substance,

calculating the PDF for each of the samples,

comparing the PDFs of the samples to the PDFs of known solid forms of the substance, and

identifying those samples that have a PDF different from that of the known solid forms.

4. A method of screening for different solid forms of a substance, which comprises

grouping a plurality of X-ray powder diffraction patterns of the substance by similarity into two or more groups,

averaging each group to generate a composite X-ray powder diffraction pattern for each group,

calculating the PDF of each composite pattern, and

comparing the PDFs to determine which groups represent the same or different solid forms.

5. A method of screening for different solid forms of a substance, which comprises

grouping a plurality of X-ray powder diffraction patterns of the substance by similarity into two or more groups,

sorting the X-ray powder diffraction patterns in each group from most to least similar,

calculating the PDF of the most and least similar X-ray powder diffraction pattern of each group, and

comparing the PDFs to determine which groups represent the same or different solid forms.

6. A method of analyzing X-ray powder diffraction patterns, which comprises

averaging two or more similar X-ray powder diffraction patterns to generate a composite pattern, and

calculating the unit cell parameters or a PDF of the composite pattern.